

Hyperostosis cranialis interna

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Hyperostosis cranialis interna

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Hyperostosis cranialis interna

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Voor papa en mama

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Part I

**General introduction on hyperostosis cranialis
interna and sclerosing bone dysplasias with
craniofacial involvement**

Chapter 1

Outline of the thesis and general introduction

Hyperostosis cranialis interna (HCI) is a unique genetic bone disorder, which has never been documented in other individuals than those described in this thesis. It is a disorder in which intracranial hyperostosis and osteosclerosis occur at the level of the skull base and the skull cap. It was in the eighties that the first patient was investigated because of bilateral facial palsies, chronic headaches and decreased unilateral vision. Because of a predominant history of facial palsies, her family members were invited to be investigated as well¹. Other important symptoms are also sequelae of bony entrapment of cranial nerves, especially diminished hearing and balance (vestibulocochlear nerve), facial pain or diminished facial sensation (trigeminal nerve), loss of smell (olfactory nerve) and visual problems (optic nerve). Furthermore headache was reported by several patients.

The severity of the symptoms and also the fascinating principle that a bone disorder is present only in the skull and seemingly completely absent in the rest of the body, made it a valuable topic for further research.

Aim of the thesis

The aim of this thesis is roughly twofold. On the one hand it has been our goal to investigate and meticulously describe the disorder clinically in order to counsel and treat patients as good as possible. On the other hand we actively participated in the translation of clinical research into genetic and biomedical research. Understanding the disorder genetically and biomedically eventually serves clinical practice, but is also crucial to contributing in the understanding of physiological processes in the human body and the understanding of the pathophysiology of diseases.

In **chapter 2**, hyperostosis cranialis interna is compared to other sclerosing bone dysplasias with involvement of the craniofacial area. Clinical, genetic and pathophysiological aspects are discussed. The embryology and ossification of the skull and skull base are described. Chapter 2 should be seen as an extension of the introduction. From here on, the thesis focuses solely on HCI. Part II is devoted to the clinical and imaging features of HCI. **Chapter 3** describes the symptomatology of HCI: the course and severity of the different symptoms. This can be seen as a sequel to the first article on HCI dating 1990¹.

In **chapter 4** the results and value of several clinical function tests are presented. The results of tone and speech audiometry and auditory brainstem responses are presented. Furthermore the results of tests evaluating trigeminal, facial and vestibular nerve functions are discussed.

In chapter 5 and 6 imaging results are reported. In **chapter 5** we present the results of the computed tomography (CT) study. On the one hand it is about the specific findings on CT in the different areas of the skull and skull base. On the other hand,

densitometric measurements have been performed to examine the bone quality and degree of calcification of the affected bone. To determine the metabolic activity in the affected bone – compared to other osseous references sites in the same individuals as well as control subjects – a study with Positron Emission Tomography was performed as described in **chapter 6**. It is one of the first studies performed with the tracer ^{18}F -fluoride in a bone disease with such a slow course. Histopathologic findings are illustrated in **chapter 7** along with the results of investigating markers of bone metabolism in blood of patients and non-affected family members.

Chapter 8 in part III of the thesis is performed in collaboration with the department of Medical Genetics at the University of Antwerp, Belgium. The possible genetic relationship with similar genetic bone dysplasias is examined. Furthermore, the disease-causing area in the genome is determined by a linkage analysis study.

In part IV two case reports describe treatment possibilities, but also important limitations. They both address to the management of sequelae of impaired nerves within the internal auditory canal. **Chapter 9** is about internal auditory canal decompression in a young patient and **chapter 10** is about a longstanding bilaterally deaf patient who came too late for this decompression. A functional solution in the form of an auditory brainstem is presented, along with the significant imposed risks due to the primary pathology.

Chapter 11 (part V) discusses the value of the results of our research and offers recommendations for further research and clinical practice. A summary of the thesis is given in **chapter 12**. In the addendum the results of an ongoing study of the department of Medical Genetics in Antwerp are presented.

Remark: a family pedigree is used in several chapters to clarify the family composition and to visualise which individuals have undergone different tests. The pedigree has undergone several changes during the past years since the study has started in 2007 because of ageing of young family members. It has been decided that the different versions of the pedigrees of each chapter within this thesis were not changed from their original version at the time the particular chapter was submitted as an article. Moreover the order of the chapters as they appear in this thesis is not chronological (see publication date of each chapter). At last it is important to realise that a genetic diagnosis has only become possible after the successful linkage analysis, which is depicted in the pedigree of chapter 8. (Unpublished) results of this study were completed in July 2011.

General Introduction

The human skull

The human skull consists of three parts: the *neurocranium* surrounds and protects the brain and the brainstem, the *viscerocranium* (also called the splanchnocranium or facial skeleton) supports and houses the organs of the face and there is the mandible.

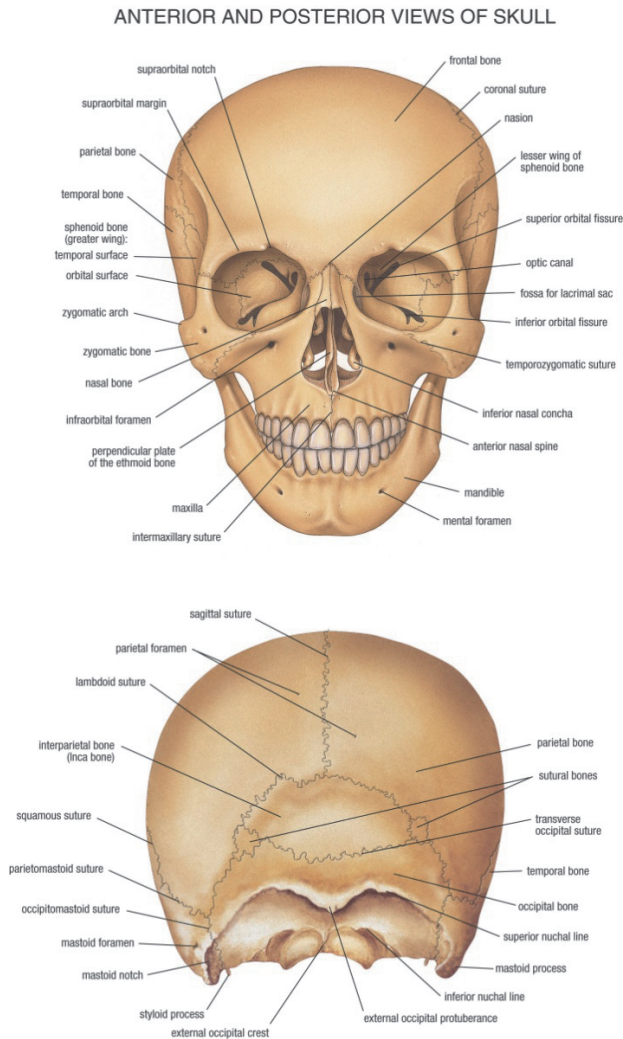


Figure 1.1 Human skull from anterior and posterior. Source: <http://infothread.org>.

Except for the lower jaw (mandible) and the middle ear ossicular chain, all the other bones of the cranium are connected by sutures permitting some flexibility. The sutures are wide and open in childhood, allowing the brain to expand during growth, and close gradually in adulthood when growth is completed.

The skull gives protection to the vulnerable underlying brain. In 1943, in an article in the *Lancet*, it was quoted that it takes about 1 ton to reduce the diameter of the skull by 1 cm². No reference was given within the article and the source – especially in this era – could therefore be called questionable. However, generally serving in a protective nature, the strength of the skull can sometimes be a drawback. In case of disproportional increase of the content of the skull relative to its volume, the intracranial pressure rises. This happens in case of intracranial bleeding (haemorrhage), oedema (in case of altitude sickness, metabolic disorders, concussion), an intracranial tumour or hydrocephalus. Increased intracranial pressure can lead to neurological symptoms such as headache, diminished consciousness, coma and eventually death.

Increased intracranial pressure occurs also in case of limited growth of the skull in childhood. For example, this occurs in patients with Crouzon syndrome, Apert syndrome and Pfeiffer syndrome: whereas the brain gradually increases in size, the skull sutures close too early, preventing the skull to grow further.

The last mechanism possibly causing increased intracranial pressure is when the cranial vault gradually becomes smaller as is the case in HCL. In some other hyperostotic bone disorders the skull becomes pathologically enlarged as well leaving less space for its content (these disorders will be discussed in detail in chapter 2).

Cranial nerves and cranial neuropathy

Except for the cranial nerves, all human nerves arise from the spinal cord. There are 12 pairs of cranial nerves, all arising from the brain. The first and the second pair, *olfactory* and *optic* nerves (for the sense of smell and sight respectively), arise directly from the cerebrum, all others arise from the brainstem. The function of the cranial nerves are as follows (within the scope of the context, some minor functions are omitted):

The *oculomotor* (III), *trochlear* (IV) and *abducens* (VI) nerves innervate the eye muscles, the upper eye lid and the circular muscles of the iris.

The *trigeminal* (V) innervates the largest chewing muscle, but its major function is sensation of the facial area. It consists of three major branches, all serving different parts of the face (frontal nerve, infraorbital nerve and submandibular nerve).

The *facial* (NVII) nerve is the nerve that innervates most facial muscles, making smiling, blinking and knitting one's brows possible. It also receives the sense of taste from the anterior two-thirds of the tongue and provides secretory innervations to the major salivary glands (except the parotid gland) and the lacrimal glands.

The *vestibulocochlear* (VIII) nerve arises as a single nerve from the brainstem, but divides into two major branches heading for their end organs within the inner ear: the vestibular nerve (balance nerve, detecting change of translation and rotation) and the cochlear nerve (hearing nerve).

The *glossopharyngeal* (IX) nerve transmits taste signals of the posterior one-third of the tongue, provides secretory innervation of the parotid gland and provides sensation of the tonsils, the pharynx and the middle ear, and it plays a role regulating blood pressure. The latter component of the nerve innervates the baroreceptors of the carotid sinus and chemoreceptors of the carotid body (visceral afferent information), mediating cardiovascular and respiratory reflex responses.

The *vagus* (X) nerve innervates most muscles in the pharynx and the larynx, making swallowing and phonation possible. It also has an important autonomic function (90% of the fibers is afferent): parasympathetic fibers to nearly all thoracic and many abdominal viscera.

The *accessory* (XI) nerve serves the sternocleidomastoid and the trapezius muscle (pure motor function).

The *hypoglossal* (XII) nerve innervates most muscles of the tongue.

All cranial nerves have in common that they pass a bony canal (neuroforamen) in the skull base on their course to the end organ (Table 1.1). In hyperostotic bone disorders the cranial nerves are potentially vulnerable, as they can be encroached at those locations. Much more common is cranial neuropathy (single or multiple nerves) due to infection, (autoimmune) inflammation or due to a tumour in the course of the particular nerve. Infectious causes are for example *Borrelia burgdorferi*, herpes zoster, varicella zoster, HIV, tuberculosis. Important inflammatory causes are sarcoidosis, Guillain-Barré syndrome and multiple sclerosis. Cholesteatoma and chronic otitis media pose the facial and vestibulocochlear nerves at risk. Tumours causing cranial nerve dysfunction can be either benign (schwannoma, glomus tumour, meningioma) or malignant (primary tumour or metastasis) and can be originating from the nerve itself or adjacent tumours with mass effect.

The facial nerve is particularly vulnerable. It meanders through the temporal bone making two curvatures, the first and second genu ("knee"), dividing it into three parts within the temporal bone: the intralabyrinthine part (along the inner ear), the tympanic part (through the middle ear) and the mastoidal part (through the mastoid bone). In physiological circumstances it is completely covered by bone – called the Fallopiian canal – starting from the exit of internal auditory canal until the stylomastoid foramen just before its intraparotid part, probably the longest neural bony canal in the body. In case of oedema due to infection or inflammation, the perineural vasculature is compromised and can cause neural dysfunction if not already caused by the pathology itself.

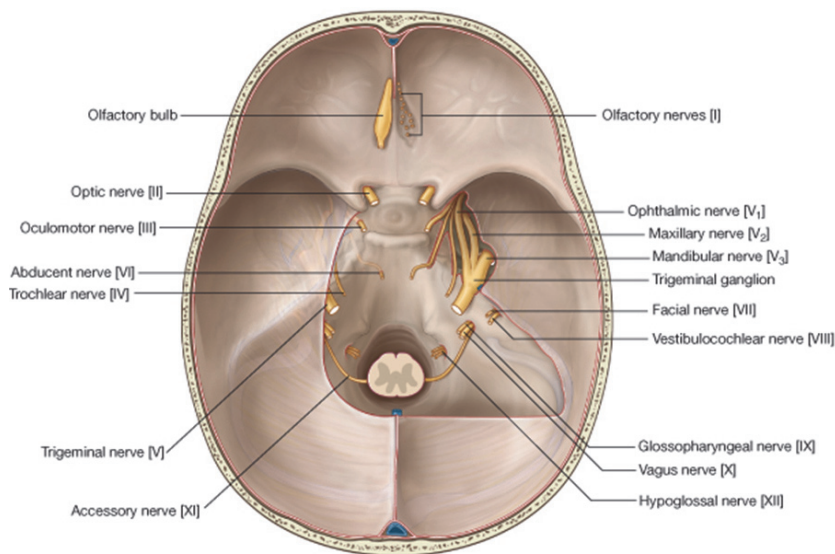


Figure 1.2 Skull base viewed from superior with all transected cranial nerves I-XII at the level of their neuroforamen. Source: Drake et al: Gray’s anatomy for Students, 2nd Edition.

Table 1.1 Cranial nerves and corresponding neuroforamina.

<i>Cranial nerve</i>	<i>Neuroforamen</i>
Olfactory	Cribriform plate
Optic	Optic canal
Oculomotor	Superior orbital fissure
Trochlear	Superior orbital fissure
Trigeminal	
Ophthalmic (first branch)	Superior orbital fissure
Maxillary (second branch)	Foramen rotundum
Mandibular (third branch)	Foramen ovale
Abducens	Superior orbital fissure
Vestibulocochlear	Internal auditory canal / Fallopien canal
Glossopharyngeal	Jugular foramen
Vagus	Jugular foramen
Accessory	Jugular foramen
Hypoglossus	Hypoglossal canal

Bone homeostasis and regulation of bone remodelling

Bone consists for 75% out of inorganic components: crystalline calcium phosphate salts (mostly hydroxyapatite $(Ca)_5(PO_4)_3OH$). The other 25% are organic components: osteoblasts, osteoclasts, osteocytes, bone lining cells and osteoid (matrix consisting

mainly of type I collagen and different other proteins³. Approximately 300 mg of calcium from the recommended daily 1,000 mg is absorbed in the duodenum and is stored as hydroxyapatite. The calcium uptake is mediated by calcitriol, the active form of vitamin D.

Types of bone tissue

Macroscopically (and also on imaging) two types of bone can be differentiated: compact or cortical bone and spongy or trabecular bone (Figure 1.3). Cortical bone is dense bone without cavities or macroscopically visible pores. Spongy bone consists of trabeculae and bone marrow between the trabeculae. There is bone marrow with haematopoietic capacity (red marrow) and without haematopoietic capacity (yellow marrow, mainly fat cells between the trabeculae). The spongy bone of the calvaria (yellow marrow) is called the diploë⁴.

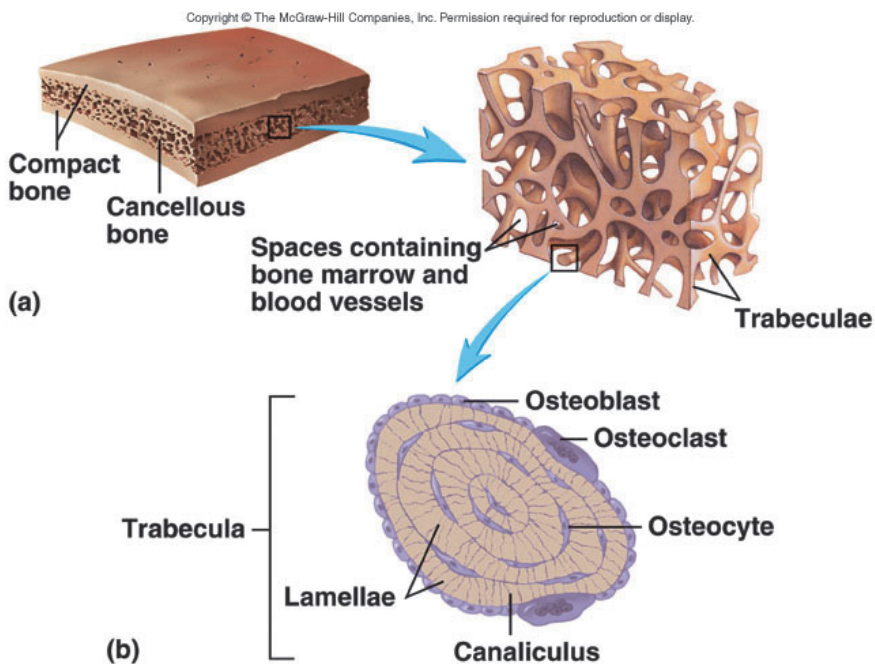


Figure 1.3 Cortical (compact) versus trabecular (cancellous) bone.

Histology and cellular structure of bone

The “organ” bone consists of several types of cells. Osteoblasts are the bone-forming cells. These are mononucleate cells originating from osteoprogenitor cells. The latter exist in the endosteum and the periosteum, the layers of connective tissue at the inner and at the outer side of bone. Osteoblasts are arranged in rows at the surface of the bone (Figure 1.3), producing the matrix material at the endosteal side consisting of collagen type I, proteoglycans and glycoproteins: osteoid. As the amount of osteoid increases, the osteoblasts lock themselves in gradually. The matrix within the osteoid calcifies, leaving only the lacunae, the places where the osteoblasts are situated. The osteoblasts are then called osteocytes. The osteoblasts at the border eventually flatten and become inactive (Figure 1.3). The then called bone lining cells serve as barrier for certain ions. The bone lining cells can be reactivated again into active osteoblasts. Osteoblasts, as well as osteocytes and lining cells all interconnect through canaliculi. There is intercellular transport of ions and small molecules through gap junctions. Osteoclasts are the bone-resorbing cells. They are cells originating from fusion of multiple granulocyte-macrophage progenitor cells in the bone marrow. They can be lined up against the border of bone that has to be degraded, often creating excavations where the matrix is “eaten away”, called the Howship’s lacunae. The bone-directed side of the cell surface of the osteoclast has a ruffled border: finger-like extensions. Within the osteoclasts there are lysosomes and secretory vesicles with collagenase and lysosomal enzymes, which can be secreted to dissolve the collagen and the calcified tissue. These phagocytic-like mechanisms are comparable to the circulating macrophages (common progenitors). Supply of bone with nutrients occurs through the many blood vessels, which are mainly situated in the aforementioned endosteum and periosteum (Volkmann’s canals).

Microscopically there are two types of organisation of bone: 1. primary or woven bone and 2. secondary or lamellar bone. Primary (woven) bone has an irregular arrangement of the type I collagen fibers, has numerous osteocytes within the matrix, with a large variation of size and shape. Primary bone is more rapidly deposited (both embryologically as well as after a fracture). Secondary bone is “mature bone” characterised by the parallel orientation of collagen fibres: lamellas (Figure 1.4). The lamellas are all situated around a Haversian canal, within which lie vessels (serving the osteocytes within the concentric layers of the matrix), nerve fibers and some connective tissue. Each separate unit with these elements is called an osteon (or haversian system), depicted in Figure 1.4. An osteon is delineated by a “kit line”, consisting of glycoproteins.

The presence of woven bone in the adult skeleton usually represents a pathological condition and indicates that reactive tissue has been produced in response to a form of stress in the bone. Slowly manufactured bone tends to be lamellar, whereas rapidly deposited bone is often woven. Often this finding correlates to the growth rate of a

bone tumour or the severity of an infection as well (fast growing → woven bone, slow growing → lamellar bone)⁵.

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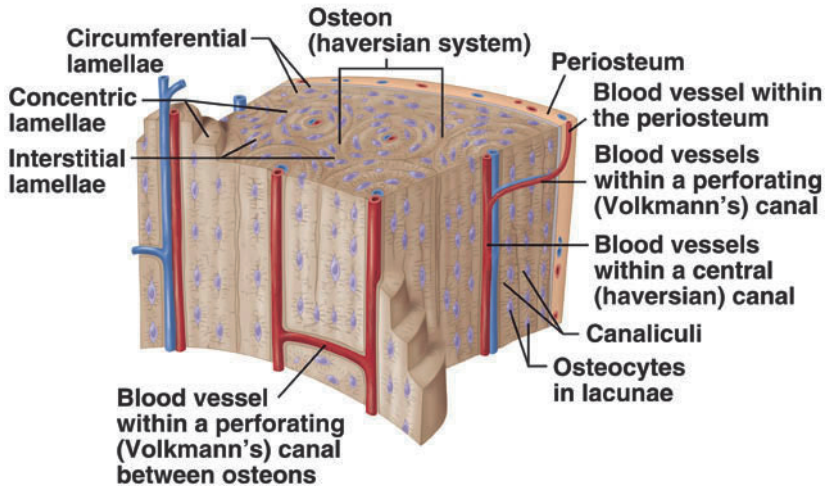


Figure 1.4 Schematic view of microscopic structure of secondary or lamellar bone.

Formation of bone

Bone can be generated in two ways: endochondral bone formation or intramembranous bone formation. In both types primary/woven bone is formed first, which is later replaced by secondary/lamellar bone. In chapter 2 this principle is applied for the bones of the skull and the mandible, illustrated with embryological images. In intramembranous bone formation bone originates directly from connective tissue, in a band shape. No cartilage is involved in this type of bone formation. The tubular bones are formed through endochondral bone formation. Endochondral ossification is the process by which the embryonic cartilaginous skeleton is replaced by bone and also the process by which most bones contribute to longitudinal growth of the body⁴.

Bone remodelling

Amongst others, bone remodelling takes place in response to bone stress. Twenty-five % of trabecular bone is remodelled each year in adults, whereas only 3% of cortical bone is remodelled yearly. This has important clinical implications: if a pathologic condition disturbs bone remodelling, preferentially bones with a high content of trabecular bone are affected, such as the femoral neck and the vertebral bodies.

Remodelling is also influenced by humoral factors regulating calcium homeostasis: parathyroid hormone, vitamin D and calcitonin. Calcium homeostasis is carefully regulated, because small changes in concentrations can have major consequences (neurotransmitters, muscle contraction). Other hormones that indirectly influence bone integrity are glucocorticoids, thyroid hormone and gonadal steroids.

The process of remodelling takes place at the level of BMUs: basic multicellular units consisting of osteoclasts and osteoblasts. Osteoblasts are responsible for bone formation, whereas osteoclasts are responsible for bone resorption. The process begins when physical or chemical signals recruit osteoclasts, starting to excavate small cavities on the bone surface. Resorption of bone by osteoclasts occurs by enzymes like collagenase, creating an acidic micro-environment (lactic acid, carbonic acid, proton pump). This causes dissolution of the hydroxyapatite (chemical formula: $\text{Ca}_5(\text{PO}_4)_3\text{OH} \rightarrow 5\text{Ca}^{2+} + 3\text{PO}_4^{3-} + \text{OH}^-$). After approximately three weeks cytokines are released from the dissolved bone matrix and begin to stimulate osteoblast proliferation, differentiation and activation. The osteoblasts eventually replace the osteoclasts in the lacunae with concentric layers: lamellae of unmineralised organic matrix (the so-called osteoid). As the cavities are filled with new osteoid, various factors essential for the process of mineralisation are secreted by the osteoblasts: alkaline phosphatase and calcium binding proteins. After mineralisation of the osteoid, osteoblasts flatten and form a layer of lining cells over the newly formed bone⁶.

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Chapter 2

Other sclerosing bone dysplasias with craniofacial involvement

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Abstract

In this review we provide a complete overview of the existing sclerosing bone dysplasias with craniofacial involvement. Clinical presentation, disease course, the craniofacial symptoms, genetic transmission pattern and pathophysiology are discussed. There is an emphasis on radiologic features with a large collection of CT and MRI images. In previous reviews the craniofacial area of the sclerosing bone dysplasias was underexposed. However, craniofacial symptoms are often the first symptoms to address a physician. The embryology of the skull and skull base is explained and illustrated for a better understanding of the affected areas.

Introduction

Genetic bone dysplasias are a rare group of disorders varying in clinical presentation, severity, genetic transmission pattern and course. Differentiation and diagnosis have been facilitated by radiological and especially genetic diagnostics, but are often still extremely challenging. The craniofacial area is often involved in these disorders, leading to functional symptoms such as cranial nerve dysfunction, aesthetic problems in case of visual disfigurement and possibly life-threatening neurological symptoms in case of disturbed cerebrospinal fluid circulation or increased intracranial pressure. The goal of this paper is to review the craniofacial aspects of the sclerosing bone dysplasias to increase familiarity with both clinicians and researchers. The few papers reviewing this group of bone dysplasias only superficially discuss the craniofacial symptoms. Many papers present cases with (outdated) X-rays of the skull presenting very unspecific information such as “increased density of the skull base”. We collected different craniofacial CT and MRI images of these disorders to show the radiologic characteristics of different disorders in order to facilitate diagnosis and to link pathophysiology/radiology to the clinical presentation.

1. Normal formation and structure of the skull bones

The skull can be roughly divided into two parts: the neurocranium and the viscerocranium. The neurocranium comprises the brain with the calvaria and skull base. The viscerocranium is the facial skeleton containing the end organs or “viscera”: the eyes, the mouth and the nose. The neurocranium consists of the frontal bone (os frontale), the occipital bone (os occipitale), the ethmoid bone (os ethmoidale), the sphenoid bone (os sphenoidale), two parietal (ossa parietale) and two temporal bones (ossa temporale). The earliest ossification has been reported at as early as 8 weeks gestational age, both in the calvaria, as well as in the facial bones¹. Phylogenetically, the base of the skull is one of the oldest parts of the human skeleton, the development sharing many similarities with other more primitive organisms². The organs of the viscerocranium and the neck originate mainly from the five pairs of pharyngeal arches, each with an outer covering ectoderm, an inner covering endoderm and a core of mesenchyme (derives from mesoderm and elements of the neural crest and the somitomeres)³.

1.1 Early embryology

The embryologic origin of the facial and cranial skeleton have been extensively documented. At first, as early as in 1828, the germ-layer theory was adhered, stating that the craniofacial skeleton was of mesodermal origin⁴. The mixed origin of the

mesenchyme was discovered at the end of the 19th century when reports appeared about ectodermal involvement: mesenchymal cells in the head were believed to be derived from the ectoderm ('ectomesenchyme' or "mesectoderm") via what was later discovered (Wilhelm His 1868, chick embryos⁵) to be the neural crest⁶. The neural crest eventually gives rise to different cell lineages: melanocytes, smooth muscle, neurons and glia and *craniofacial cartilage and bone*⁷. The quail-chick chimaera technique introduced by Nicole Le Douarin has learned us a lot about cell migration during the development of the (avian) embryo^{8,9}. Using this technique, (part of) a host chick's neural tube and neural crest cells are replaced with a donor quail's neural tube and neural crest cells, making it possible to investigate the developmental fate of cells within an embryo (using immunohistochemical staining). This technique confirmed that ectoderm (or better: the neural crest) is the main contributor to the embryogenesis of the vertebrate head. In 1993, the complete embryological origin of the avian skull was 'mapped' by Couly¹⁰. The frontal, parietal and squamosal bones, part of the otic capsule and the complete facial skeleton derive from the neural crest. Only the occipital bones, a major part of the otic capsules and the posterior part of the sphenoid bone are of mesoderm and somitic origin (Figure 2.1).

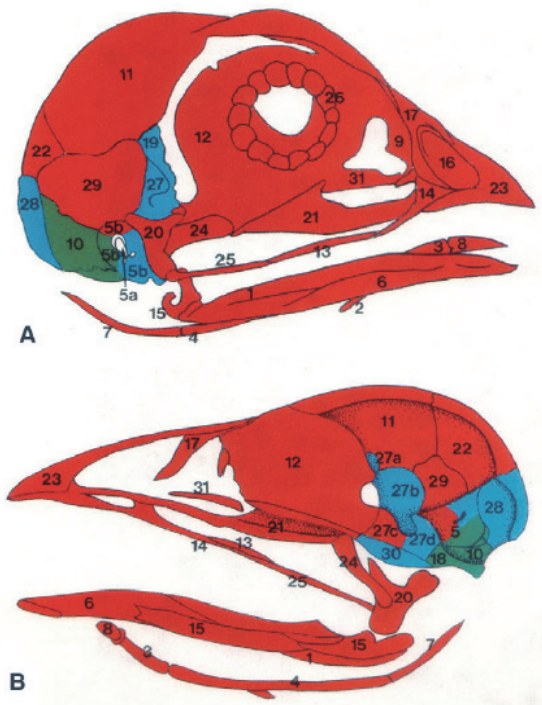


Figure 2.1 Schematic drawing of cephalic skeleton of bird (published in 1993 by Couly), republished with permission. A: Right external view. B: Right internal view. Red, skeleton of neural crest origin; blue, skeleton of cephalic mesoderm origin; green, skeleton of somitic origin¹⁰.

1.2 Ossification of the cranial base and the calvaria

Eventually becoming the skull base, neural crest cells form paired cartilaginous plates as early as in the fourth week of gestational age. This is when the development of the craniofacial skeleton becomes spatially conceivable (Table 2.1, Figure 2.2). The most important cartilaginous plates are the prechordal, the hypophyseal, the lateral and the parachordal cartilages¹. Endochondral ossification occurs from posterior to anterior, starting in the occipital area at 12 weeks and progresses laterally. Ossification in the orbitosphenoid and the alisphenoid (deriving from the first pharyngeal arch, vide infra section 1.3) starts at approximately 15-16 weeks forming the lesser and greater wings of the sphenoid bone respectively. The eventual derivatives of the cartilaginous centers are perfectly outlined in the study of Nemzek². In Figure 2.3 the contrast between the two types of ossification is displayed by specifically stained foetal transections.

Table 2.1 Ossification of the anterior and posterior skull base (reprinted and modified with permission of the American Journal of Neuroradiology²). The origin of the major osseous structures are outlined. The different ossification centers are visualised in Figure 2.1.

<i>Endochondral Ossification</i>		
Embryonic cartilage	Foetal Cartilage	Derivative
* Occipital bone		
Parachordal cartilage	A. Basioccipital	• Anterior clivus
	B. Exoccipital	• Anterior occipital condyle
		• Hypoglossal canal
		• Posterior occipital condyle
		• Jugular tubercle
	C. Supraoccipital	
*Sphenoid bone		
Hypophyseal cartilage	A. Postsphenoid or basisphenoid	• Body sphenoid (posterior to tuberculum)
		• Posterior clivus
		• Sella turcica
		• Dorsum sellae
Prechordal cartilage (anterior to notochord)	B. Presphenoid	• Body sphenoid (anterior to tuberculum)
		• Mesethmoid cartilage (perpendicular plate of ethmoid, crista galli)
Lateral cartilage	C. Orbitosphenoid	• Lesser sphenoid wings
		• Anterior clinoids
		• Planum sphenoidale
	D. Alisphenoid	• Greater wing (with foramen rotundum, ovale and spinosum)
	E. Medial pterygoid	
<i>Intramembranous ossification</i>		
Orbital plate frontal bones, greater wing sphenoid (lateral part), lateral pterygoid plate, squamous occipital bone, palatine bone		

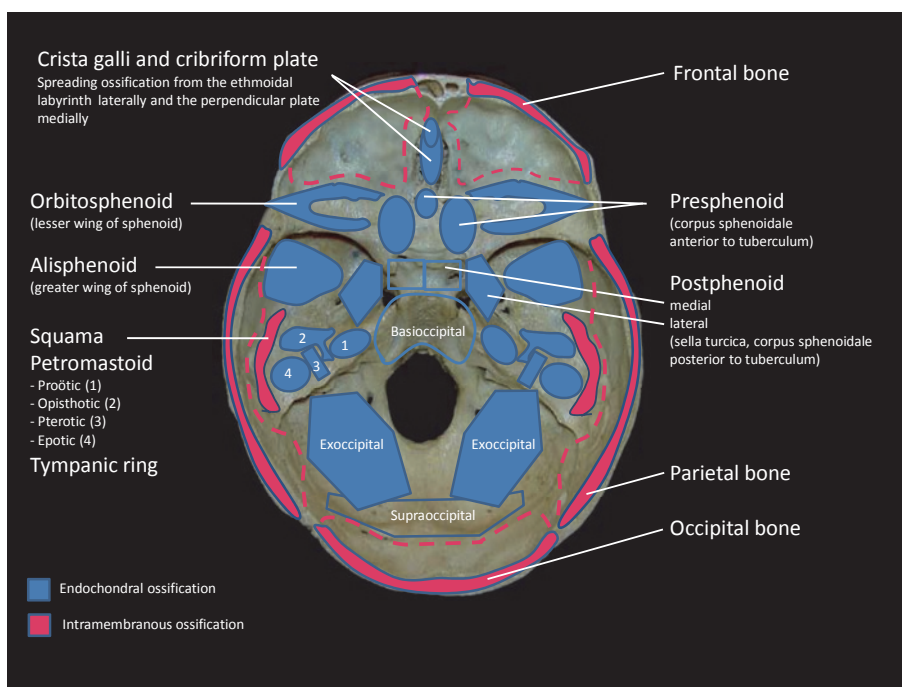


Figure 2.2 Schematic representation of calvarial and skull base ossification (reprinted and modified with permission of American Journal of Neuroradiology²). The contrast between intramembranous and endochondral is illustrated with the same colours as in Figure 2.3.

Although the ethmoid is part of the eventual anterior skull base, it is ossified within the cartilage of the nasal capsule. It is formed by three centers. There are two lateral centers that ossify first. They form what are called the labyrinths, giving rise to the ethmoidal cells, the lamina papyracea and middle turbinates (conchae media). After birth the third center starts ossifying, giving rise to the perpendicular plate (lamina perpendicularis) of the nasal septum and the crista galli (fusion takes place after approximately one year). The cribriform plate (lamina cribriformis) is ossified partly from the perpendicular plate and partly from the labyrinths.

Hardly any intramembranous ossification takes place in the skull base (only the orbital plate of the frontal bones, the lateral part of the greater wing of the sphenoid (ala major), the lateral pterygoid plate (lamina pterygoidea lateralis) and the squamous part of the occipital bone).

The squama of the occipital bone is developed in membrane, the rest is developed from cartilage.

The parietal bone is ossified in membrane from a single center, which appears at the parietal eminence about the eighth week of foetal life. Ossification gradually extends in a radial manner from the center toward the margins of the bone.

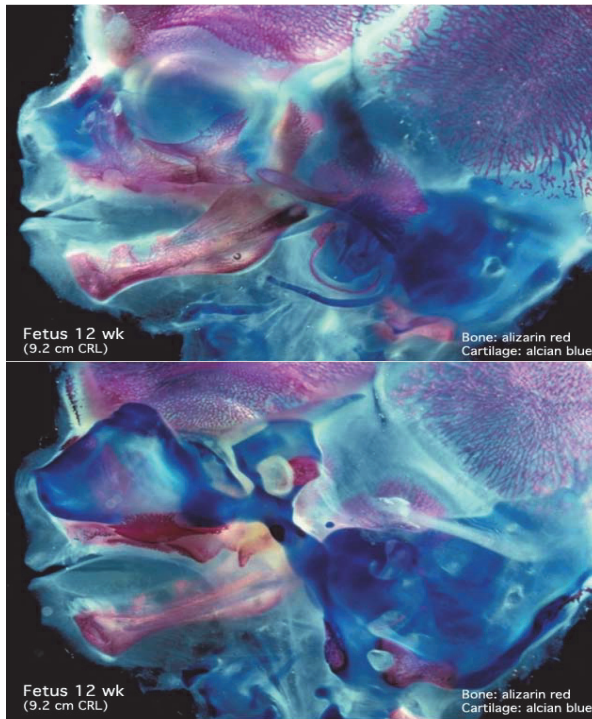


Figure 2.3 Both pictures are of the same 12-week-old human foetus head, double stained to show both cartilage (blue) and newly-formed bone (red). Both types of ossification (endochondral and intramembranous) in separate regions of the skull are displayed. In the upper - lateral (external) view, note the distribution of new bone formation by intramembranous ossification in the plates of the cranial vault, temporal bone, orbit, upper jaw (maxilla) and lower jaw (mandibula) regions. In the lower- medial (internal) view, note the distribution of cartilage from the nasal region to the base of the skull and the atlas/axis showing where endochondral ossification takes place (with new bone forming) (Reprinted with courtesy of prof. Diewert).

The frontal bone is formed through intramembranous ossification with one primary center on each side, supraorbitally. Ossification starts here at the end of the second month; it spreads cranially (calvarial bone) and internally/horizontally (orbital plate). The middle part is formed through endochondral ossification centers, one on each side of the middle line. The nasal parts and zygomatic processes form in a similar way.

The embryology of the temporal bone (*os temporale*) is extremely complicated (Fig. 2.2). It is formed out of skull base ossification centers and the first and second branchial arches (ossicles, styloid part of the petrous bone). The squamous part is formed through intramembranous ossification. The two other main parts of the temporal bone are the petromastoid part and the tympanic ring. The middle ear cavity, the mastoid, the otic capsule and the petrous apex originate from four ossification centers: the proötic (roof and front of medial petrous part, part of cochlea, part of vestibule, superior semicircular canal and medial wall of tympanic cavity), the opisthotic (promontory of the cochlea, floor of the tympanic cavity and vestibule, carotid canal, lower and lateral part of the cochlea and inferior part of the medial petrous part), the pterotic (roof of tympanic cavity and antrum) and the epiotic centers (mastoid process and posterior semicircular canal). The otic capsule is the first bone to be formed in this area endochondrally, except for the modiolus of the cochlea and the spiral lamina. The otic capsule keeps its avascular structure throughout life and is not replaced by Haversian bone. Ossification of the otic capsule takes place roughly between week 16 and 23¹¹⁻¹³. The last part of the temporal bone is the tympanic ring, which eventually encircles the tympanic membrane and later forms the bony part of the external ear canal.

1.3 Ossification of the viscerocranium

The first pharyngeal arch is responsible for formation of the precursors of the maxillae and the mandible: the maxillary and the mandibular prominences, containing central cartilaginous components called the palatopterygopalate bars and the Meckel's cartilages respectively. Although the abovementioned cartilages suggest that the maxilla and mandible ossify in an endochondral way, both develop in membrane. These cartilages are retained and surrounded by intramembranous bone formation covering the outer surfaces of the Meckel's cartilage. The maxillae form from two ossification centers (one for the maxilla, one for the premaxilla)¹⁴. Moreover, the maxillary cartilage forms the alisphenoid (mentioned before in section 1.2) and the incus, and the mandibular cartilage forms the malleus (endochondral)³.

The other pharyngeal arches do not contribute to the craniofacial skeleton, except for the styломastoid processes and the stapes, both from the second pharyngeal arch.

The lacrimal bone ossifies from a single center (endochondral), as well as each nasal bone. The nasal septum initially originates as one cartilaginous plate, the ethmovomerine cartilage. The upper part ossifies into the perpendicular plate (part of the ethmoid, *vide supra*), two ossifying centers (one on each side) form the vomer. The palatine bone ossifies in membrane from a single center, the zygomatic bone also ossifies in membrane from three centers: one for the malar part, two for the orbital part.

2. Positioning of the sclerosing bone dysplasias

In earlier days there was significant overlap between the different (craniofacial) sclerosing bone dysplasias, caused by the difficulty of differentiation. The lack of diagnostic modalities like computed tomography, molecular and genetic research contributed to this problem. This led to considerable confusion in the nomenclature and classification of this group of disorders. Initially all the sclerosing bone dysplasias were given the name **osteopetroses**. The first report was published as *Marble bone disease* in 1904 by Albers-Schönberg¹⁵. After this, numerous single cases were reported in literature, also referred to as Albers-Schönberg disease (Figure 2.4). In 1926 Karshner named this seemingly single entity osteopetrosis¹⁶. Later, this group appeared to be a very heterogeneous group of disorders. In the 1960s, a differentiation was made between “benign” (autosomal dominant) and “malignant forms” (autosomal recessive)¹⁷. In the review of Beighton (1977)¹⁸, the first attempt was made to differentiate different osteopetroses: 1. Dominant and recessive forms of *osteosclerosis* with dominating bone sclerosis instead of changes in bone configuration (accounting both the cranium and the tubular bones), 2. *Craniotubular dysplasias*: abnormality of modelling of long bones associated with sclerosis of the cranium and 3. *Craniotubular hyperostosis*: skeletal deformity resulting from bony overgrowth.

In modern times dozens of different bone dysplasias have been described, all categorised within different subgroups, the most recent overview having been published by the International Skeletal Dysplasia Society¹⁹. In Table 2.2 an overview is given of the characteristics and features of the disorders which are discussed within this review.

June 20, the entire mandible (Fig. 2) came out through the submental opening, while dressings were being changed. Its expulsion was not followed by bleeding. Fig. 3 shows the opening six weeks later, with the tongue protruding through it.

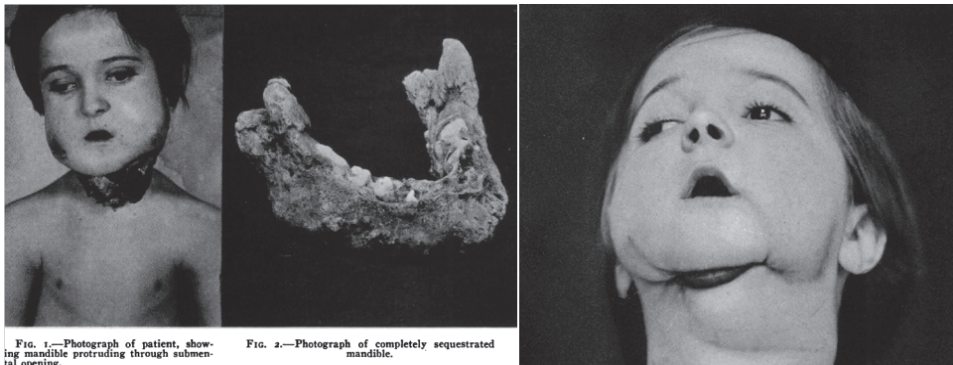


FIG. 1.—Photograph of patient, showing mandible protruding through submental opening.

FIG. 2.—Photograph of completely sequestered mandible.

Figure 4.4 Photos of a patient with “Marble bone disease” in one of the first publications in 1934¹⁶. The original text illustrates the impotence of the physicians.

Table 2.2 Overview of sclerosing bone dysplasias with significant craniofacial involvement.

Disorder	Transmission pattern	Cytogenetic localisation	Gene	Protein function
<i>Disorders due to decreased bone resorption</i>				
<u>Autosomal recessive osteopetroses</u>				
OPTB1: severe neonatal or infantile form	AR	11q13.2	TCIRG1	Subunit of ATPase proton pump
OPTB2: intermediate form (osteoclast-poor)	AR	13q14.11	RANKL	TNF ligand superfamily
OPTB3: with renal tubular acidosis	AR	8q22/8q21.1	CA2	Carbonic Anhydrase 2
OPTB4: severe neonatal or infantile form	AR	16p13.3	CLCN7	Chloride channel
OPTB5: infantile form, with nervous system involvement	AR	6q21	OSTM1	Osteopetrosis associated transmembrane protein
OPTB6: intermediate form	AR	17q21.31	PLEKHM1	Pleckstrin homology domain-containing protein
OPTB7: infantile form, osteoclast-poor with immunoglobulin deficiency	AR	18q21.33	RANK	Receptor activator of NF-kappa-B
OPTB8: infantile form	AR	7p15.2	SNX10	Sorting Nexin 10
<u>Autosomal dominant osteopetroses</u>				
OPTA1/ADO1: late-onset form type 1	AD	11q13.4	LRP5	Lowdensity lipoprotein receptor-related protein 5
OPTA2/ADO2: late-onset form type 2 (Albers-Schönberg disease)	AD	16p13.3	CLCN7	Chloride channel 7
Dysosteosclerosis	AR	10q22.1	SLC29A3	Nucleoside transporter lysosomes
Pycnodysostosis	AR	1q21	CTSK	Cathepsin K
Craniometaphyseal dysplasia	AR or AD	AR: 6q21–22 AD: 5p.15.2	AR: unknown AD: ANKH	Pyrophosphate transmembrane transport, extracellular inhibitor of mineralisation
<i>Disorders due to increased bone turnover</i>				
Paget's disease of bone	AD	5q35.3	SQSTM1	Sequestosome 1
Osteoectasia with hyperphosphatasia (Juvenile Paget's)	AR	8q24.12	OPG	Osteoprotegrin
<i>Disorders due to increased bone formation</i>				
LRP5-related bone dysplasias/High bone mass phenotype (including Worth disease and endosteal hyperostosis)	AD	11q13.4	LRP5	LDL receptor-related protein 5
Van Buchem disease	AR	17q21.31	SOST	Sclerostin, osteocyte-produced negative regulator of bone formation (inhibition of the WNT pathway)
Sclerosteosis	AR	17q21.31	SOST	Sclerostin
Progressive diaphyseal disease (Camurati–Engelman)	AD	19q13	TGFB1	TGF-beta-1
Osteopathia striata with cranial sclerosis	XD	Xq11.1	WTX	Inhibition of the WNT pathway
Craniodiaphyseal dysplasia	AD	17q21.31	SOST	Sclerostin
Raine syndrome	AR	7p22.3	FAM20C	FAM20C kinase limits bone formation
<i>Conditions with exclusive skull involvement</i>				
Hyperostosis cranialis interna	AD	8p21	?	?
X-linked calvarial hyperostosis	XR	Xq27.3-Xqter	?	?

Pathogenesis	Calvaria	Skull base	Described CN involved	Facial bone	Onset
					Prenatal Childhood
Different defective mechanisms in osteoclast metabolism leading to decreased osteoclastic activity (e.g. defective acidification for bone matrix dissolution, defective osteoclast differentiation, defective chloride transport)	Calvaria, skull base and facial bones affected in all types of osteopetroses to a different degree, OPTB1, -4, -5 and -8 being the most severe forms (mostly lethal at young age), OPTB2 and -6 the least severe. Involvement of cranial nerves 2,5,7,8,9,10 and 11 described				Childhood Early childhood Prenatal Childhood Childhood Early childhood
No longer considered as osteopetrosis as due to increased bone formation	Yes	Yes (mild)	2,5,8	No	Childhood
As in AR osteopetroses	Yes (mild)	Yes	1,2,5,7,8	No	Late childhood
Impaired lysosyme function, secondary impaired osteoclast differentiation/function	Yes, not pronounced	Yes	2,8	Yes	Childhood
Decreased collagen degradation due to Cathepsin K deficiency	Mild	Mild	-	Mild	Childhood
Defective osteoclastogenesis due to disturbed pyrophosphate transmembrane transport	Yes	Yes	2,3,4,7,8	Yes	Childhood
Hyperplasia and hypertrophy of osteoclasts	Yes	Yes	8	Yes	>40 years
Enhanced osteoclast activity	Yes	Yes	2,8	No	Childhood
	Yes	Yes	7,8	Yes	Generally childhood
Due to increased WNT signalling	Yes	Yes	1,5,7,8,12	Yes	First decade
	Yes	Yes	2,5,7,8	Yes	Childhood
Increased osteoblast activity and decreased bone resorption	Yes	Yes	1,2,5,7,8	No	Childhood
WNT pathway is a mediator in cell–cell interactions during embryogenesis and tissue regeneration	Yes	y/n	2,5,6	Yes	Childhood
Due to increased WNT signalling	Yes	Yes	2,7,8	Yes	Birth or childhood
Abnormal phosphorylation of small integrin-binding ligand n-linked glycoproteins	Yes	Yes	-	Yes	Birth
Unknown	Yes	Yes	1,2,5,7,8	Exostoses mandible	Childhood
Unknown	Yes	No	-	Yes	First year

Table 2.2 (continued)

Disorder	Craniofacial complications/facial appearance
<i>Disorders due to decreased bone resorption</i>	
<u>Autosomal recessive osteopetroses</u>	
OPTB1: severe neonatal or infantile form	Range of symptoms possible in different osteopetroses: frontal bossing, macrocephaly, jugular foramen and intratemporal carotid canal narrowing (severe cases), prognathism, dental malocclusion, intracranial calcifications, hydrocephalus, mandibular osteomyelitis, hydrocephalus, sleep apneas
OPTB2: intermediate form (osteoclast-poor)	
OPTB3: with renal tubular acidosis	
OPTB4: severe neonatal or infantile form	
OPTB5: infantile form, with nervous system involvement	
OPTB6: intermediate form	
OPTB7: infantile form, osteoclast-poor with immunoglobulin deficiency	
OPTB8: infantile form	
<u>Autosomal dominant osteopetroses</u>	
OPTA1/ADO1: late-onset form type 1	Arnold Chiari (and possibly CN IX–XII dysfunction), ↑ intracranial pressure
OPTA2/ADO2: late-onset form type 2 (Albers-Schönberg disease)	Stomatologic problems, especially osteomyelitis mandible
Dysosteosclerosis	Frontal bossing, mid-facial hypoplasia, sleep apneas
Pycnodysostosis	Craniosynostosis, delayed suture closing, obtuse mandibular angle, blue sclerae, dental abnormalities
Craniometaphyseal dysplasia	Prognathism, hypertelorism, frontonasal bossing (all due to hyperostosis), hydrocephalus
<i>Disorders due to increased bone turnover</i>	
Paget's disease of bone	Middle ear pathology, jaw deformity, gingival problems
Osteoectasia with hyperphosphatasia (Juvenile Paget's)	Macrocephaly, loss of teeth
<i>Disorders due to increased bone formation</i>	
LRP5-related bone dysplasias/High bone mass phenotype (including Worth disease and endosteal hyperostosis)	Torus palatinus, mandibular hyperostosis
Van Buchem disease	Large mandible and skull, middle ear pathology, increased intracranial pressure
Sclerosteosis	Calvarial and mandibular overgrowth, increased intracranial pressure
Progressive diaphyseal disease (Camurati–Engelman)	Headache
Osteopathia striata with cranial sclerosis	Cleft palate/Pierre Robin sequence, recurrent otitis media, hypertelorism, frontal bossing, low-set ears, hydrocephalus
Craniodiaphyseal dysplasia	Hydrocephalus and narrowed foramen magnum, hypertelorism, torus palatinus, nasolacrimal duct obstruction, choanal obstruction
Raine syndrome	Microcephaly, frontal bossing, proptosis, depressed nasal bridge, and midface hypoplasia
<i>Conditions with exclusive skull involvement</i>	
Hyperostosis cranialis interna	Increased intracranial pressure
X-linked calvarial hyperostosis	Lateral and frontal horns, flat nasal root, short upturned nose

Other skeletal features	Extraskeletal features
<i>Tendency to fracture, accounts for all AR osteopetroses</i> Erlenmeyer flask deformity long bones	Anaemia due to bone marrow suppression caused by hyperostosis of the cortical bone, and extramedullary haematopoiesis (secondary hepatosplenomegaly); tubular acidosis in OPTB3
Erlenmeyer flask deformity long bones	
Pelvis, ribs, spine almost unaffected Spinal endplate thickening, fractures, osteomyelitis, bone-within-bone appearance iliac wings Short stature, platyspondyly, metaphyseal sclerosis, diaphyseal widening and demarcated osteosclerosis Tendency to fracture, brachydactyly Secondary osteoporosis (AD)	Developmental retardation, epilepsy, red-violet skin spots Short stature, mental retardation (AR)
Involvement proximal femurs, the pelvis and lumbar spine, "bowing" bones Tendency to fracture, short stature, kyphoscoliosis, bowed extremities, diaphyseal thickening	None Muscular weakness, (psycho)motoric retardation, retinal degeneration
Endosteal sclerosis of diaphyses, sclerosis pelvis	Hydrocephalus/cerebrospinal tract abnormalities, Arnold–Chiari malformation
Hyperostosis clavicles, ribs, diaphyses of the tubular bones,	None
Syndactyly/brachyphalangy, gigantism Pain in extremities, diaphyseal and later on metaphyseal hyperostosis Metaphyseal striations tubular bones	Syringomyelia Muscle weakness, pubertas tarda Heart defects, retardation
Diaphyseal hyperostosis	Syringomyelia
Subperiosteal hyperostosis, chondrodysplasia punctata, sagittal vertebral clefting, intervertebral disc calcifications	Intracranial and intrarenal calcifications, multiple visceral malformations
None None	None None

3. Conditions with significant involvement of the skull

3.1 Disorders due to decreased bone resorption

Osteopetroses

Osteopetroses (Figure 2.5) are generalised bone dysplasias. All share features of increased bone density caused by a decreased bone resorption by osteoclasts with diffuse sclerosis of the spine and the tubular bones with metaphyseal widening. There are eight types of autosomal recessive (AR) osteopetroses (OPTB1-8) and two types of autosomal dominant osteopetroses (OPTA1 and OPTA2 or ADO 1 and ADO2). The prevalence of OPTA2 is estimated between 0.2 and 5.5/100,000^{20,21}, OPTA1 has been published about 30 times (2012), and the prevalence at birth of “malignant” autosomal recessive osteopetrosis is 0.75/100,000²². OPTB3, also called osteopetrosis with renal tubular acidosis, has been described 50 times. Two genetic recessive forms are clinically called intermediate osteopetroses (OPTB2 and OPTB6), which have a milder course than the other AR forms of the disease^{23,24}. The autosomal recessive subtypes are the most severe forms, often leading to stillbirth or early death. The clinical symptoms can include increased fracture rate, delayed tooth eruption, hydrocephalus, progressive neurodegeneration, pancytopenia, hepatosplenomegaly and extramedullary haematopoiesis, the last three due to displacement of bone marrow by hyperostosis²⁵. For some AR forms, haematopoietic stem cell transplantation is the important treatment although this cannot rescue the neurodegeneration. Autosomal dominant types are milder and generally present in adulthood (Table 2.2).

In the craniofacial area there is thickening of the calvaria in all types of osteopetrosis, most distinct in malignant AR forms and OPTA1, less pronounced in OPTA2 and the intermediate AR forms. These differences were determined in a radiological study in which the patients were diagnosed clinically, not genetically²⁶. Skull base involvement is less severe in OPTA1 compared to OPTA2. Of the cranial nerves, the optic nerve is affected most often. Optic canal stenosis is seen regularly leading to partial or complete blindness, especially in AR osteopetrosis. There is discussion whether this is caused by direct optic nerve compression or by obstruction of venous orbital outflow causing papilloedema²⁷. In AR osteopetrosis, jugular foramen and intratemporal internal carotid artery stenosis have been described, not in the AD form. All the following symptoms can occur both in the AR as well as in the AD forms: not only facial palsy and (conductive) hearing loss (due to Eustachian tube encroachment), but also sensorineural hearing loss (mainly internal auditory canal narrowing). Tonsillar herniation secondary to decreased intracranial volume is common. Meningoencephalocoele has been described spontaneously in children with open fontanels, but also after decompressive craniotomies²⁶. In our opinion after studying the numerous reports in literature, no distinction can be made between the different types of osteopetrosis on the basis of the affected cranial nerves.

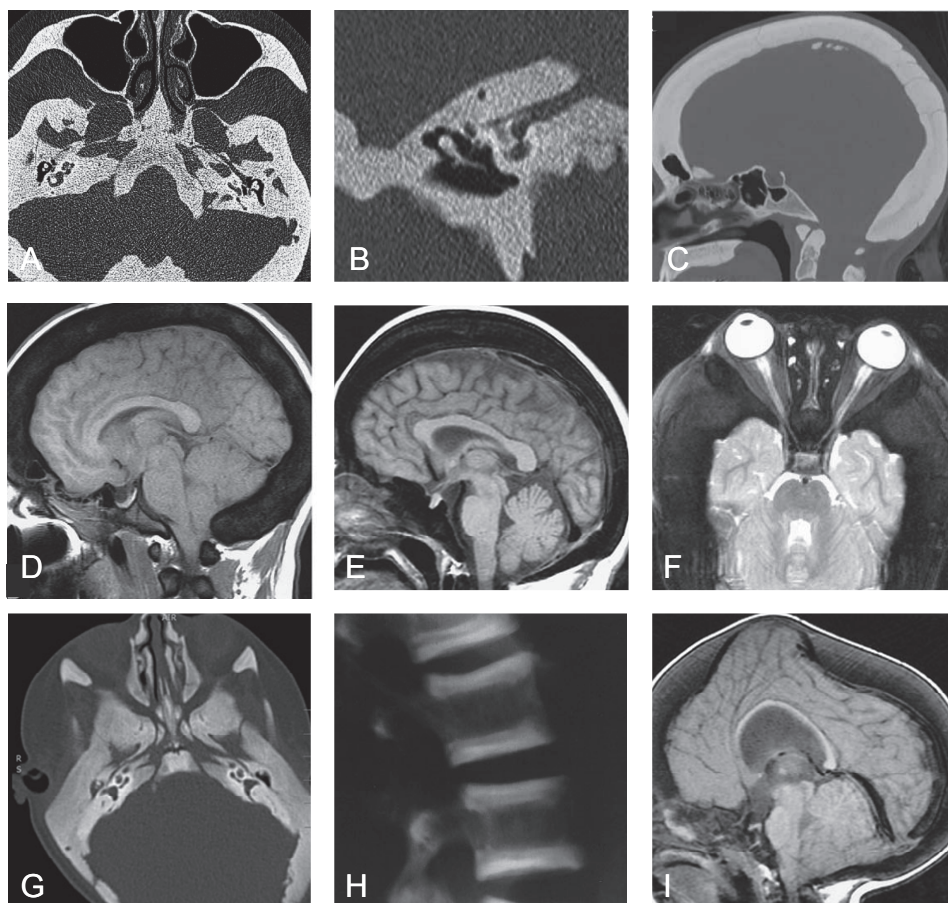


Figure 2.5 Osteopetroses. A: Axial CT of a 44-year-old lady with osteopetrosis, not stated which subtype (most probably autosomal dominant subtype). Marked thickening of the calvaria with loss of the diploë, unaffected facial bones, B: Coronal reconstruction at the level of the right temporal bone of the same patient. Normal middle ear aspect, narrowed internal auditory canal¹⁴². C: Sagittal reconstruction of CT of a 25-year-old woman with ADO1 or intermediate autosomal dominant osteopetrosis. Note the skull base including the clivus is not affected. D: Sagittal T1-weighted MRI of a patient with ADO1 shows thickening of the calvaria with cerebellar tonsillar ectopia. E: Sagittal T1-weighted MRI of a patient with ADO2 with significant more skull base involvement, compare the smaller sella turcica to E. F: Axial T2-weighted MRI image in autosomal recessive osteopetrosis shows optic canal stenosis and optic nerve atrophy¹⁴³. G: Axial CT scan of 9-month-old girl with autosomal recessive osteopetrosis. There is obstructive hydrocephalus. Note the narrowed nasal cavity and the thick calvaria for the age¹⁴⁴. H: Lateral radiograph of the spine showing a sandwich-like sclerosis of the vertebral endplates¹⁴⁴. I: Sagittal T1-weighted image in a paediatric patient with ARO shows a spontaneous meningoencephalocele into the anterior fontanel¹⁴³.

In most types of autosomal recessive osteopetrosis there is a normal or even an increased number of osteoclasts (osteoclast-rich osteopetrosis), however the osteoclasts have an impaired capacity to acidify the extracellular compartment between the osteoclast and the bone tissue (of the primary spongiosa)²⁸. This acidic environment is essential in the normal physiology for the dissolution of bone matrix. The underlying defect causing this problem can be loss of function mutations in carbonic anhydrase II, a subunit of the vacuolar proton pump (encoded by *TCIRG1* gene) or the chloride channel *CICN7* or its β -subunit *OSTM1*²⁹⁻³⁴. Recently, mutations in Sorting Nexin 10 (*SNX10*) were found in patients with autosomal recessive osteopetrosis. *SNX10* is suggested to interact with the vacuolar proton pump^{35,36}. In addition one form of osteopetrosis was found to be due to mutations in the *PLEKHM1* gene with putative involvement of vesicular transport in the osteoclast²⁴. Two subtypes are due to abnormal osteoclast differentiation resulting in an osteoclast-poor form of osteopetrosis. Mutations were found in the genes encoding the osteoclast receptor RANK and its ligand RANKL^{28,37}.

Two distinct radiological phenotypes of AD osteopetrosis have long been described³⁸. Further studies characterising the two AD osteopetroses at the clinical, biochemical, histological, and biomechanical level revealed that these corresponded to two distinct disorders, OPTA1 and OPTA2³⁹. However unravelling the underlying molecular defects indicated that OPTA1 is rather due to an increased bone formation instead of decreased bone resorption (see below, high bone mass phenotype⁴⁰). Therefore, technically this form can be removed from the category of osteopetroses. OPTA2 represents the classical form of Albers-Schönberg disease. It presents with a milder phenotype compared to the recessive forms but with a high variability. Also the penetrance is reduced to 60-80%. The genetic defects are heterozygous missense mutations in the *CLCN7* gene⁴¹.

Dysosteosclerosis

In dysosteosclerosis (Figure 2.6F), an autosomal recessive disorder, there is generalised osteosclerosis (ribs, clavicles, scapulae, mid-diaphyses) presenting in childhood, a tendency to fractures and a short stature. 17 cases have been described up to date⁴². The main craniofacial feature is skull base sclerosis. Thickness of the calvaria is normal in most cases. Blindness due to compression of the optic nerve in the optic canal is described. Often, cases are diagnosed as osteopetrosis, however patients with dysosteosclerosis generally do not have anaemia. Sensorineural hearing loss and facial nerve palsy are not reported in the children with dysosteosclerosis. There is often mental retardation and also dental problems are described (oligodontia, delayed eruption of primary teeth)^{42,43}. The prognosis is poor: all reported cases die in childhood; only one adult patient has been reported⁴². CT or MRI images of the craniofacial area are not available in the literature, but sclerosis of the mandible, maxillae, mastoids is described.

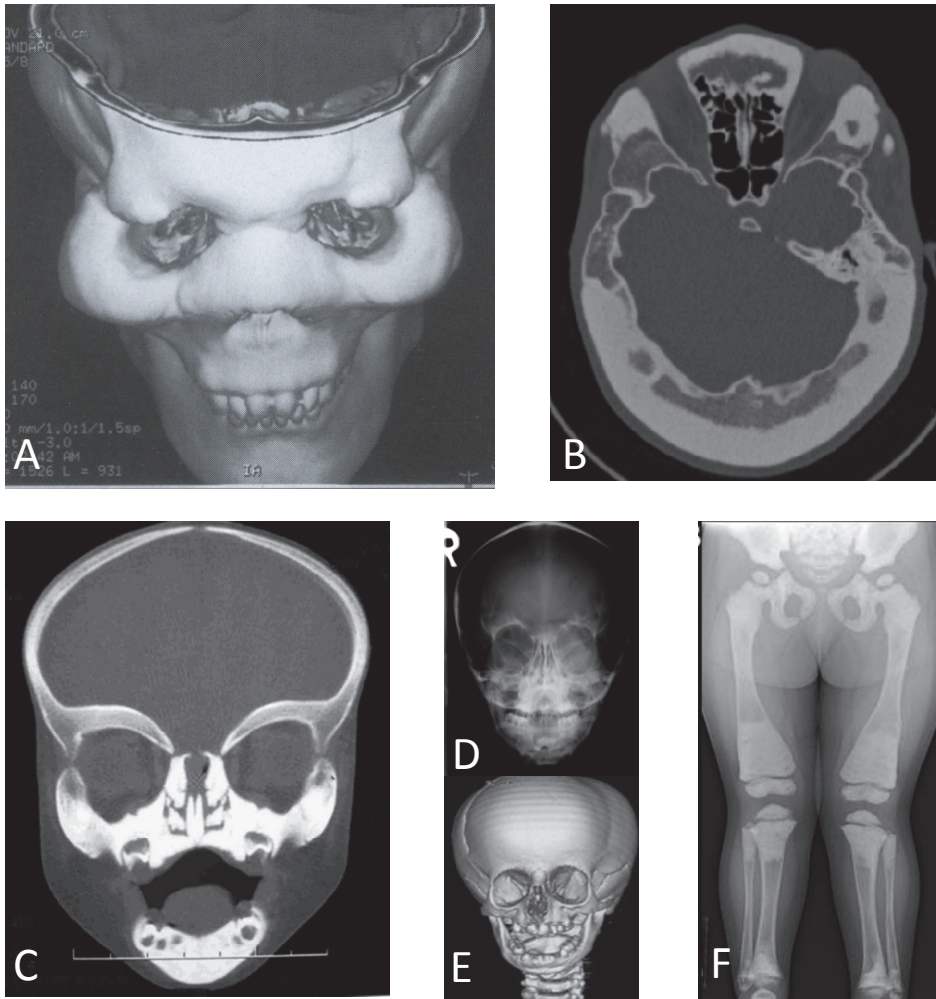


Figure 2.6 A-C: **Craniometaphyseal disease**. 3D-CT scan (A) showing the marked frontal, nasal and zygomatic bossing, causing facial disfigurement⁵⁸. B is a preoperative scan of a patient – probably with the autosomal recessive form - undergoing “skull reduction” and C illustrates the fact that nasal obstruction is one of the commonest features in this disorder¹⁴⁵. D-E: **Pycnodysostosis**. D shows the dense maxilla⁴⁷, E shows mandibular hypoplasia and skull dysplasia due to craniosynostosis¹⁴⁶. F: **Dysosteosclerosis**. Dramatic metaphyseal expansion and osteosclerosis⁴⁵. No illustrative images of the craniofacial area could be found.

Only recently, a common gene defect in the *SLC29A3* gene has been found in two cases of dysosteosclerosis⁴⁴. This gene encodes a nucleoside transporter. Mutations in this gene are associated with other conditions without significant skeletal involvement: pigmented hypertrichosis with insulin-dependent diabetes (PHID) and H syndrome (skin

hyperpigmentation and hypertrichosis, hepatosplenomegaly, heart anomalies, hearing loss, hypogonadism and low stature). SLC29A3 is expressed in osteoclasts. Since a reduced number of osteoclasts have been demonstrated in vivo and in vitro in patients, this protein is probably involved in osteoclast differentiation and function⁴⁵.

Pycnodystostosis

Pycnodystostosis (Figure 2.6D-E) is an autosomal recessive skeletal dysplasia, first described by Maroteaux and Lamy in 1962 and also called Toulouse-Lautrec syndrome, after the French artist who was thought to be affected⁴⁶. It is a rare disorder with less than 200 cases reported since 1962. The incidence is estimated at 1.7 per one million births⁴⁷. The disorder usually becomes symptomatic in childhood, often at the time of a fracture. The clinical features include short stature, increase in the bone density of long bones, pathological fractures with poor healing, stubby hands and feet with dystrophic nails, blue sclera and skull deformities with delayed suture closing, a mandible with an obtuse angle, dental abnormalities and acro-osteolysis⁴⁶⁻⁴⁸. Often there is mild calvarial and skull base osteosclerosis without obvious hyperostosis. No cranial nerve involvement has been described.

Mutations in the *CTSK* gene are responsible for pycnodystostosis. This gene was mapped to chromosome 1q21 by genetic linkage analysis and subsequently identified as coding for Cathepsin K by a positional cloning strategy⁴⁹⁻⁵¹. *CTSK* is critical for osteoclast-mediated bone resorption and is highly expressed in osteoclasts. It is responsible for the degradation of bone matrix proteins like type I collagen, osteopontin and osteonectin. Dissolution of inorganic matrix and degradation of organic matrix occur in the extracellular lysosome under low pH conditions⁴⁸. *CTSK* deficiency does not affect the function of osteoclast-mediated extracellular acidification, but the ability of osteoclasts to degrade collagen is impaired rather than the demineralisation of the extracellular matrix^{52,53}. A total of 33 different mutations in *CTSK* have been reported in 59 families with pycnodystostosis, including 23 missense mutations, 4 frameshift mutations, 3 nonsense mutations, 2 splicing mutations and one termination codon mutation⁴⁸.

To date, there is no specific treatment available. Bone fractures are an important threat to patients with pycnodystostosis. It is quite important to establish a correct diagnosis as early as possible to prevent fractures and ensure a better quality of life⁴⁸.

Craniometaphyseal dysplasia

This is one of the disorders with marked craniofacial involvement (Figure 2.6A-C). It usually becomes symptomatic in young childhood. Craniometaphyseal dysplasia (CMD) exists in an autosomal recessive and autosomal dominant form, in total seventy cases have been published²². This distinction was first made clinically by Gorlin in 1969, with the autosomal dominant form being less severe⁵⁴. Nurnberg and colleagues uncovered the genetics of autosomal dominant CMD^{55,56}. The locus for autosomal recessive CMD

was mapped by lughetti in 2001⁵⁷. Interestingly, in CMD the facial bones (mandible, maxilla, frontal bones) are mostly affected leading to a dysmorphic appearance. In the autosomal dominant form the craniofacial features are apparent: facial distortion and cranial nerve compression. The autosomal recessive type is characterised by an even more extensive form of sclerosis of the cranial bones. Choanal narrowing, nasal and nasolacrimal duct obstruction are often observed in both types. The skull base becomes sclerotic with marked frontonasal hyperostosis (resulting in frontal and paranasal bossing) and optic, facial and vestibulocochlear nerve involvement have been reported. Also 3rd and 4th cranial nerve impairment have been described⁵⁸. The progression of the disease often stabilises in adult patients. Typically there is mixed or conductive hearing loss due to fixed ossicles or a fixed footplate and potentially a narrowed internal auditory canal. Often there is also hyperostosis in the middle ear cavity, causing chronic otitis media due to Eustachian tube dysfunction^{59,60}. The long bones show flaring and abnormal modelling of the metaphyses.

In the autosomal dominant form there is a mutation in the *ANKH* gene (5p15.2) coding for the ankylosis (ANK) multi-pass transmembrane protein⁵⁵. ANK has a function in maintaining the balance between intracellular and extracellular pyrophosphates. Pyrophosphate is a regulator of bone matrix mineralisation. Low concentrations of extracellular pyrophosphate (as hypothesised in CMD) supposedly lead to an excess of hydroxyapatite deposition, whereas high concentrations promote calcium pyrophosphate dehydrate crystal formation⁶¹. There is some evidence that there is explicit osteoclast dysfunction or reduced osteoclastogenesis in CMD^{62,63}. The recessive form of CMD was mapped to chromosome 6q21-22, however the responsible gene has not yet been discovered^{57,64}.

3.2 Disorders due to increased bone turnover

Paget's disease of bone

Among the sclerosing bone disorders, Paget's disease of bone (PDB, osteitis deformans or better osteodystrophia deformans, Figure 2.7A-E) is the commonest of all, with an incidence of more than 2% in the elderly within affected populations⁶⁵. Onset before the age of 40 is very rare. It is primarily an osteoclast disease. The disease is characterised by focal regions of increased bone remodelling, with abnormalities in all phases of the remodelling process. The pathogenesis is not yet completely understood, but is multifactorial with genetic, nongenetic and environmental factors playing a role⁶⁶. One gene has been identified being the Sequestosome 1 (*SQSTM1*) gene with a mutation found in 2.5-10% of the sporadic cases and 40-50% of the patients with familial history⁶⁷. Furthermore genetic association studies revealed the presence of several susceptibility loci. The most common skeletal sites of Paget's disease are: proximal part of femurs, pelvis and lumbar spine. The disease is asymptomatic in most cases, but can lead to bone pain, deformities, pathological fractures or neurological

deficits⁶⁶. The inheritance appears to be autosomal dominant with variable penetrance in some families. There are also some indications that there is a role for viral aetiology⁶⁸. Histologically, an increased number of enlarged osteoclasts can be seen with too many intracellular nucleoli and typical intranuclear inclusions that are similar to nucleocapsids of paramyxoviruses⁶⁸. In the early stage there is excessive bone resorption. Radiologically, this can be recognised as osteolytic lesions. Subsequently, new bone is deposited by osteoblasts, often sclerotic and poor of quality, potentially causing the symptoms. This is recognised on CT imaging as cotton wool appearance of the involved bone caused by the replacement of normal marrow with disorganised bone of low mineral density.

The skull is involved in approximately 70% of cases of Paget's disease. Involvement of the mandible or maxillary bones may result in jaw deformity, malocclusion, and periodontal disease. Often there is frontal bossing. Hearing loss is common in Paget's patients with affected temporal bones. Patients often have mixed hearing loss with high-frequency sensorineural hearing loss and a (low-frequency) air-bone gap⁶⁹. Tinnitus is often reported as well. Histopathological studies have demonstrated microfractures within the otic capsule⁷⁰. Other plausible causes of sensorineural hearing loss and vestibular impairment are involvement of the endosteal layer of the otic capsule, leakage of toxic substances into the endolymph (such as lysosomes) or possibly endolymphatic hydrops due to blockage of the cochlear and endolymphatic duct due to hyperostosis. The aetiology of the conductive hearing loss is debated. Because usually the ossicles are not affected, the conductive hearing loss could be caused by stapedial fixation. Third window lesions due to the microfractures could also contribute to conductive hearing loss (and on the same time lead to supranormal bone conduction thresholds)⁷¹. Facial nerve palsy has not been reported in Paget's disease but it is plausible that any cranial nerve can be affected when it is damaged by a Pagetic bone lesion.

Paget's disease is generally treated medically with bisphosphonates (or salmon calcitonin). Hearing is reported to stabilise after treatment⁷².

Juvenile Paget's disease

Hyperphosphatasia with osteoectasia, juvenile Paget's disease or chronic idiopathic hyperphosphatasemia is an autosomal recessive disorder with macrocephaly, elevated serum alkaline phosphatase and most have a short stature (Figure 2.7F-J). It was first described in 1956⁷³ and approximately 50 cases have been described in the literature²². There is pronounced involvement of the tubular bones (widening of the diaphyses and bowing) and the vertebrae, having an osteoporotic demineralised aspect with tendency to fracture. There is a wide range of clinical severity, classified as severe (onset first 18 months), intermediate (onset after 2 years) or mild, correlating with the type of mutation⁷⁴. Affected children often display failure to thrive, progressive loss of muscular strength with delayed walking (mild/intermediate) or failure to walk (severe).

There is calvarial hyperostosis (with a wide diploic space) and skull base thickening. Deafness is reported (even at the age of 2), both conductive (middle ear hyperostosis) as well as sensorineural (internal auditory canal encroachment) nature has been mentioned^{75,76}. Extensive sinonasal involvement has also been described⁷⁷.

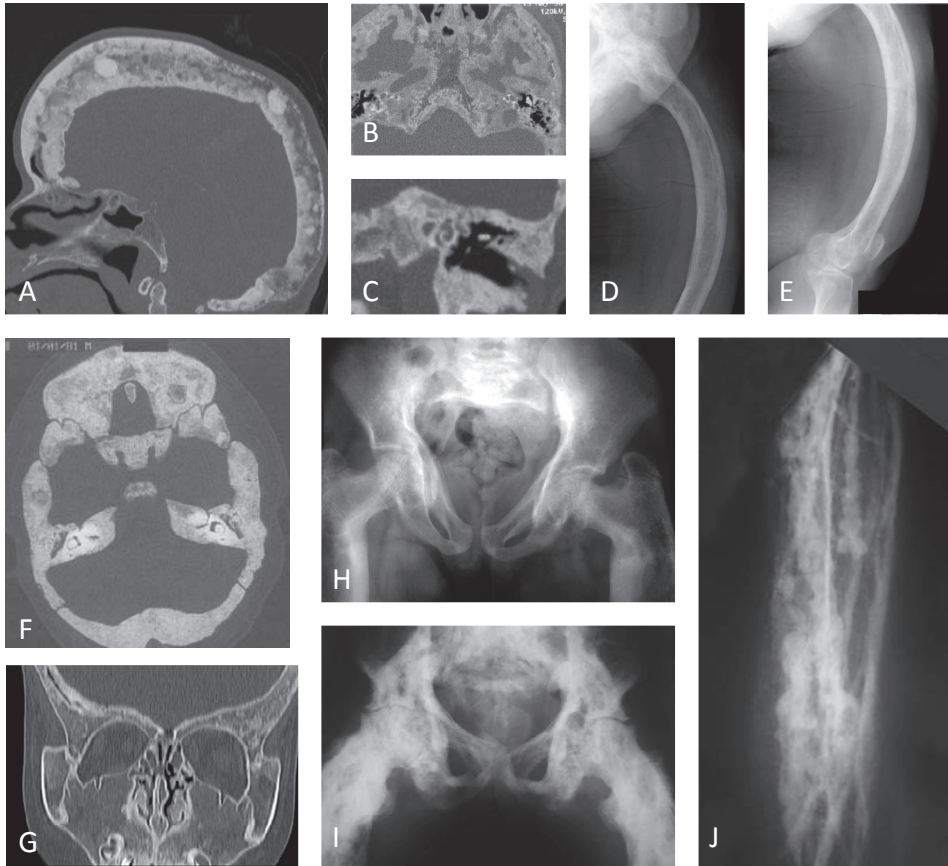


Figure 2.7 Disorders with increased bone turnover. **A-E: Paget's disease of bone.** A: Sagittal CT reconstruction. Frontal bossing and the so-called cotton wool aspect of bone. B: Axial CT image at the level of the skull base showing gross osteolytic lesions especially at the level of the clivus. The middle ear area is spared, the inner ears are involved¹⁴⁷. C: Coronal reconstruction in the same patient with a severely damaged inner ear¹⁴⁸. D and E: Frontal and lateral femur radiographs of an 81-year-old patient. Typical bowing and thickening of the cortices. **F-J: Osteoectasia with hyperphosphatasia (Juvenile Paget's).** F: Axial CT of 17-year-old man with severe generalised skull base hyperostosis⁷⁶. G: Coronal CT image of a 25-month-old. Severe hyperostosis of the maxillar bones and the turbinates⁷⁷. H: Pelvic AP radiograph (age 10 years) showing markedly widened femoral diaphyses, with thickening of the medial cortex¹⁴⁹. I: Radiograph of the pelvis of a 45-year-old man showing extreme radiodensity with coarsening of the trabeculae. There is severe osteoarthritis of the hips. J: Same patient as F, AP radiograph of the tibia. The entire shaft is expanded (due to medullary expansion) and there are broad longitudinal radiodense striations¹⁵⁰.

Juvenile Paget's patients have a mutation in the *TNFRSF11B* gene which encodes osteoprotegerin (OPG), a member of the superfamily of tumour necrosis factor receptors. This receptor plays an important role in balancing the bone turnover. OPG belongs to the important OPG/RANK-L/RANK system that regulates osteoclastogenesis⁷⁸. OPG deficiency in juvenile Paget's disease causes a negative feedback mechanism in bone turnover to fall away, leading to an increased bone turnover. Histologically there are increased numbers of osteoclasts and osteoblasts. Oral calcitonin and bisphosphonates are reported to be effective medical treatments. These inhibit bone resorption and increases bone mineral content⁷⁹.

3.3 Disorders due to increased bone formation

High-bone-mass phenotype

A spectrum of different disorders with similar phenotypes have recently been proposed to be categorised as high-bone-mass phenotype on the basis of their common pathophysiologic pathway: Worth disease, endosteal hyperostosis, autosomal dominant osteosclerosis, autosomal dominant osteopetrosis type I (see also section osteopetroses). Together, less than ten families have been described. The phenotype is similar in all patients and is characterised by dense bones and cortical hyperostosis, mainly affecting the skull and tubular bones. Further clinical findings range from asymptomatic to square jaw and torus laesions of the mandible⁸⁰. However clinical knowledge on these disorders is limited, except for autosomal dominant osteopetrosis type I which is now not considered a type of osteopetrosis anymore⁴⁰. The interest in these disorders is mainly in the genetic and biomedical field, because the responsible gene could possibly play an important role in the treatment of osteoporosis. Contemporary radiological images (other than ADO1) are not available. All disorders are caused by gain-of-function mutations in the first β -propeller domain of the LDL-receptor related protein 5 (LRP5), situated in the extracellular part of the protein⁸¹. The importance of LRP5 for bone density was initially uncovered by genetic analyses of patients with extreme bone phenotypes, like the osteoporosis pseudoglioma syndrome, an autosomal recessive disease of low bone mass⁸², and the high-bone-mass trait^{83,84}. Subsequent experiments revealed that LRP5 is required for efficient Wnt signaling and β -catenin activation in osteoblasts⁸⁵. Gain of function mutations in LRP5 disrupt the binding capacity to the extracellular inhibitors DKK1 or SOST, thus increasing bone formation. The finding that both activating and loss-of-function mutations in LRP5 have a severe effect on bone density indicate the importance of the Wnt/ β -catenin pathway in bone homeostasis⁸¹.

Van Buchem disease and sclerosteosis

Van Buchem disease (Figure 2.8A-F) was formerly known as hyperostosis corticalis generalisata familiaris and was first described by Van Buchem^{86,87}. It is most prevalent in an isolated population in the Netherlands (less than 50 patients described). The disease is characterised by periosteal hyperostosis which is clinically most evident in the skull and skull base, the mandible, the clavicles, the ribs and the diaphysis of the tubular bones. It is an autosomal recessive disorder that usually becomes symptomatic in the first decade of life. Facial and vestibulocochlear nerve deficits occur in almost all patients. Middle ear pathology due to Eustachian tube dysfunction is reported. The disease progresses during the entire life, also leading to increased intracranial pressure in some, olfactory dysfunction, trigeminal neuropathy and papilloedema⁸⁸⁻⁹⁰.

Sclerosteosis is a similar, usually even more severe, autosomal recessive craniotubular hyperostotic dysplasia⁹¹. The disease is mostly seen in the Afrikaner population in South-Africa (less than 100 cases), the first series being described in 1976 and 1979^{92,93}. Clinically, patients present with headaches, gigantism and facial dysmorphisms, including mandible overgrowth and proptosis. Calvaria and skull base hyperostosis cause increased intracranial pressure and cranial nerve entrapment of mainly facial and vestibulocochlear nerves (again, also middle ear pathology due to Eustachian tube dysfunction). Stapes fixation, round window obliteration and malleus ankylation due to adjacent middle ear hyperostosis have been documented⁹⁴. Furthermore syndactyly and brachyphalangy are seen in the majority of patients. Decompressive craniotomy/craniectomy is often necessary (second decade) due to raised intracranial pressure: in case of increased intracranial pressure first supratentorial decompression should be performed before posterior fossa decompression, in order to avoid downward pressure of the brain and secondary brainstem herniation⁹⁵. This is the same reason why lumbar puncture should never be performed in these patients with increased intracranial pressure.

In both disorders, typically there is a dense aspect of the hyperostosis, there is loss of the diploë. Eventually this results in a homogeneously thickened skull. The mastoids and possibly the sinuses become sclerotic.

In the 1970s and 1980s several articles about sclerosteosis and Van Buchem disease were published, both regarded as “craniotubular hyperostosis”. In 1984, Beighton et al. described the main clinical similarities and differences between these two disorders. They concluded that “it is tempting to postulate that sclerosteosis and Van Buchem disease are the same disorder, and that their separation is an artificial concept based upon clinical differences which are really reflections of varying expression of the same abnormal genotype”⁹⁶. Indeed, in 1998 the candidate region of the genetic defect for Van Buchem disease was localised: 17q12-q21⁹⁷. In 1999, Balemans et al. confirmed that the candidate region for the sclerosteosis overlaps the Van Buchem-region⁹⁸. In 2001, the *SOST* gene encoding sclerostin was identified and loss of function mutation was demonstrated in sclerosteosis⁹⁹. In Van Buchem disease, the mutation is a 52Kb

deletion downstream of the *SOST* gene, which causes a down-regulation of the *SOST* gene¹⁰⁰. Sclerostin is a cystine knot-containing protein secreted by osteocytes¹⁰¹. It can bind to the co-receptor LRP5/6 preventing the formation of the LRP-Fz-wnt complex and thus inhibiting the induction of Wnt-signalling. In both sclerosteosis and Van Buchem disease this impaired inhibitory feedback mechanism results in increased bone formation.

Camurati-Engelmann disease

In Camurati-Engelmann disease (also called progressive diaphyseal dysplasia) the osteoclast resorption and the osteoblastic bone formation are both disturbed (Figure 2.8G-J). It is an autosomal dominant condition (about 200 cases described²²), in which hyperostosis usually starts at the diaphyses of the femora and tibiae. Later on, it progresses to the fibulae and also the upper extremities. Typically the epiphyses are spared. The metaphyses may become affected in a later stage¹⁰². Muscle weakness, muscle wasting and limb pain are the most prominent symptoms¹⁰³. The first symptoms occur usually in childhood.

Skull base and calvarial involvement are both present in severe cases (over 50%) and an excellent overview has been given by Carlson and colleagues in a retrospective study of as much as 306 patients¹⁰⁴. Cranial neuropathy of the olfactory, optic, trigeminal and facial nerves are described, however are present in less than 5% of the patients. Hearing loss, whether conductive, mixed or sensorineural of nature is more frequent (19% in total). Chronic headache is reported in over 10%. Radiographically the skull bones look more heterogeneous and ribbed than in Van Buchem disease and sclerosteosis. The diploë is also disappeared. There is no involvement of the facial bones, except mandibular exostoses can be present.

The molecular basis of Camurati-Engelmann disease is a mutation in the *TGFB1* gene encoding the transforming growth factor β 1 molecule. TGF- β 1 normally stimulates bone formation at the periosteal side (of the diaphyses of the long bones) by osteoblasts and suppresses bone resorption by osteoclasts at the endosteal side¹⁰⁵. Most of the known mutations are thought to negatively affect the capacity of the so-called latency associated peptide to keep the mature TGF- β 1 inactive¹⁰⁶. This causes premature or facilitated activation of the mature peptide. The balance between bone formation and resorption is disturbed, causing an increase in bone formation. The phenotype of Camurati-Engelmann disease, especially obliteration of the medulla, is in line with this pathogenesis.

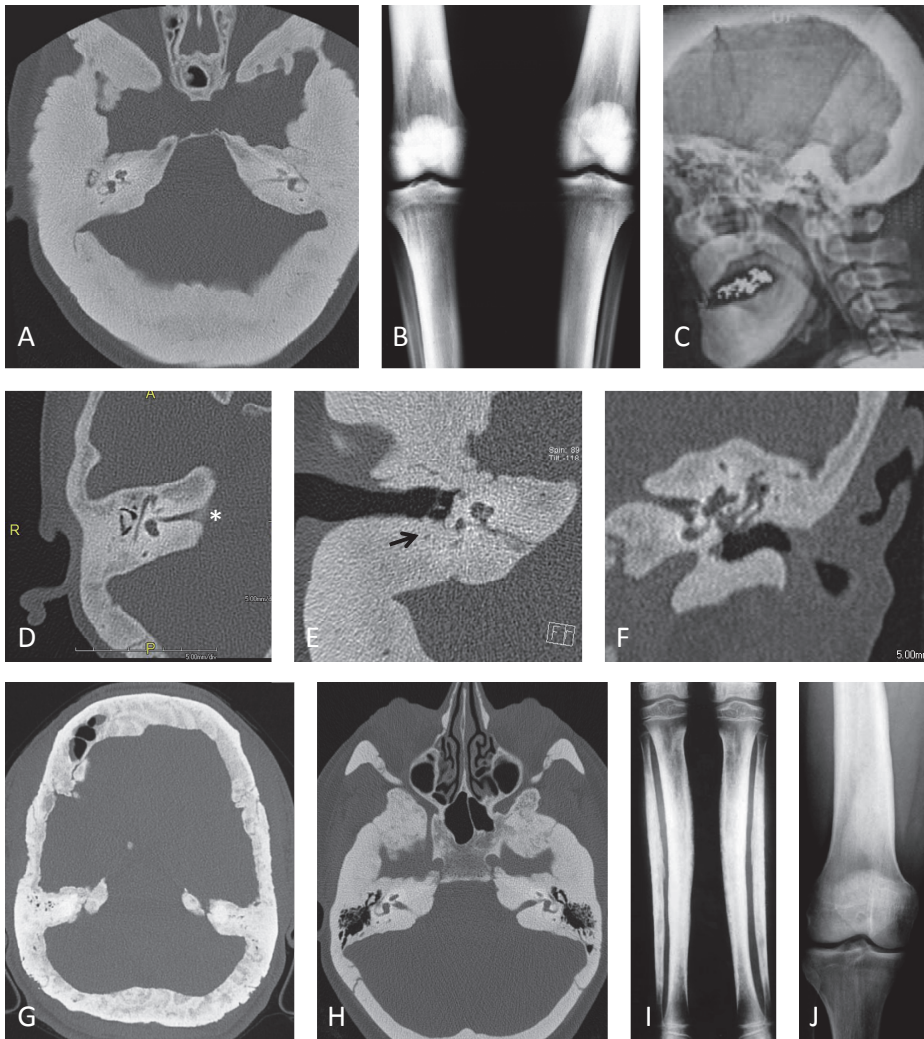


Figure 2.8 Disorders with increased bone formation (1). A-F: **Van Buchem Disease**. A: Axial CT scan of a 43-year-old man with multiple cranial nerve palsies, obvious loss of the diploë. B: AP Radiograph showing cortical thickening with narrowing of the medullary cavity, especially at the diaphyses. There are vertical striations at the diaphyses and metaphysis of the long bones, comparable to osteopathia striata⁹⁷. C: Lateral X-ray of an adult patient with typical mandibular hyperostosis. D: Axial CT of right temporal bone of an 8-year-old patient with facial nerve palsy. The middle ear and the internal auditory canal (*) are extremely narrowed. E: Axial CT of right temporal bone, same patient as A. Vertical part of the facial nerve is hardly visible (arrow). Contralateral temporal bone of D, coronal reconstruction, with middle ear inflammation due to Eustachian tube encroachment. G-J: **Camurati-Engelmann Disease**. G: Axial CT of an adult patient. There is a more heterogeneous aspect of the bone. Loss of the diploë. H: Axial CT scan at the level of the skull base. The mastoid and the middle ears are still aerated. The facial bones are spared. I: AP radiograph showing cortical thickening and a severe modelling defect at the diaphysis of both tibiae and fibulae. J: AP radiograph of a right femur, sparing of the metaphysis and epiphysis¹⁰³.

Osteopathia striata with cranial sclerosis

The name osteopathia striata with cranial sclerosis (OSCS) refers to the typical radiodense longitudinal striations at the metaphyseal regions of the tubular bones on X-ray, first described in 1924 (Figure 2.9E-H). It is an X-linked dominant disorder and also called Voorhoeve syndrome, approximately 100 cases have been described²². The striations are usually observed between five months and six years after birth, the hyperostotic skull base is often present at birth¹⁰⁷. The severity of the disease is very heterogeneous. Most of the affected individuals are symptomatic due to the “cranial stenosis”: craniofacial hyperostosis leading to dysmorphic features (enlarged nasal bridge with hypertelorism and palatal abnormalities), nasal obstruction, cranial neuropathies due to nerve encroachment by bone overgrowth, and macrocephaly are often present. Rare findings are Pierre Robin sequence, laryngotracheomalacia, holoprosencephaly, and hypoplasia of the corpus callosum. Heart defects, scoliosis, rib, and vertebral anomalies may also be present. Radiologically the striations are obvious in the tubular bones, but have also been described in the mandible and the maxilla¹⁰⁸. Conductive hearing loss usually occurs due to Eustachian tube encroachment with consecutive tympanic membrane atelectasis, and ossicular chain fixation^{109,110}. No internal auditory canal abnormalities or inner ear abnormalities have been reported, although multiple publications report on mixed or sensorineural hearing loss¹¹¹⁻¹¹⁴. None of the articles reporting on sensorineural hearing loss provide high-quality images proving disease-related cochlear or neural impairment, or originate from an era when CT scans were not yet available. To our knowledge, sensorineural hearing loss originates from chronic (disease-related) middle ear inflammation until otherwise proven. Trigeminal (maxillary branch) and oculomotor nerve deficits have been described¹¹⁴.

The abnormalities are due to increased osteoblast activity, caused by a mutation in the gene encoding for the WTX protein. WTX is an inhibitor of the canonical WNT signaling pathway, which plays an important role as mediator in cell-cell interactions during embryogenesis and tissue regeneration^{108,115}. WTX promotes β -catenin degradation. On the other hand, upon WNT stimulation, it may act as a scaffold protein promoting LRP6 phosphorylation and thus activating WNT signaling¹¹⁶. WTX has been found mutated in several types of cancer, such as Wilms tumor, acute myeloid leukemia or colorectal cancer. However, these are somatic mutations. Germline mutations or mosaicism in OSCS patients do not seem to predispose to tumour genesis^{108,117,118}.

Craniodiaphyseal dysplasia

Craniodiaphyseal dysplasia (CDD, Figure 2.9A-D) is a severe autosomal dominant disorder that presents in early childhood with a combination of neurological symptoms due to cranial abnormalities and diaphyseal tubular bone sclerosis and hyperostosis. Less than 20 cases have been described. Therapeutic options are only symptomatic and

most patients die in childhood. Neurological symptoms are secondary to massive diffuse hyperostosis of the calvaria and the skull base: CSF circulation can be severely impaired due to a small foramen magnum, leading to hydrocephalus and syringomyelia. Brain stem compression as well as cranial nerve compression (2nd, 7th and 8th) can occur¹¹⁹. Non-neurological craniofacial manifestations are choanal obstruction, obstruction of the nasolacrimal ducts and mandibular overgrowth. Hypertelorism is characteristic, torus palatinus has also been described¹²⁰. The long bones show hyperostosis and sclerosis of the diaphyses.

Only recently, craniodiaphyseal dysplasia has also been linked to the *SOST* gene. Mutations were found in two separate CDD cases, both at the same location, in the secretion signal of the *SOST* gene. It was demonstrated that these mutations prevent secretion of sclerostin, however the exact pathogenesis is not yet understood¹²¹. In CDD the hyperostosis of the facial bones is much more prominent than in Van Buchem disease and sclerosteosis. The facial aspect is referred to as “leontiasis ossea” (lion-like appearance).

Raine syndrome

Lethal osteosclerotic bone dysplasia or Raine syndrome is characterised by generalised diffuse osteosclerosis, characteristic facial dysmorphism and brain abnormalities including intracerebral calcifications. Not more than 20 reports are available and the disease is symptomatic and also generally lethal at birth or soon thereafter. There is a generalised increase in the density of all bones and a marked increase in the ossification of the skull, leading to a typical phenotype: a narrow and prominent forehead, proptosis, depressed nasal bridge, and midface hypoplasia. Bilateral choanal obstruction is described¹²². Periosteal bone formation is characteristic for this disorder. It appears to be inherited in an autosomal recessive fashion^{123,124}.

Raine syndrome is caused by mutations in *FAM20C*, which encodes a Golgi-localised protein kinase. FAM20C kinase activity is essential for limiting bone formation in humans. Members of the Small Integrin Binding Ligand N linked Glycoproteins (SIBLING) protein family can modulate biomineralisation. Their ability to do so is based on their phosphorylation status and they can be phosphorylated by FAM20C. The increased bone density of Raine syndrome patients could be accounted for by decreased phosphorylation of SIBLING proteins¹²⁵.

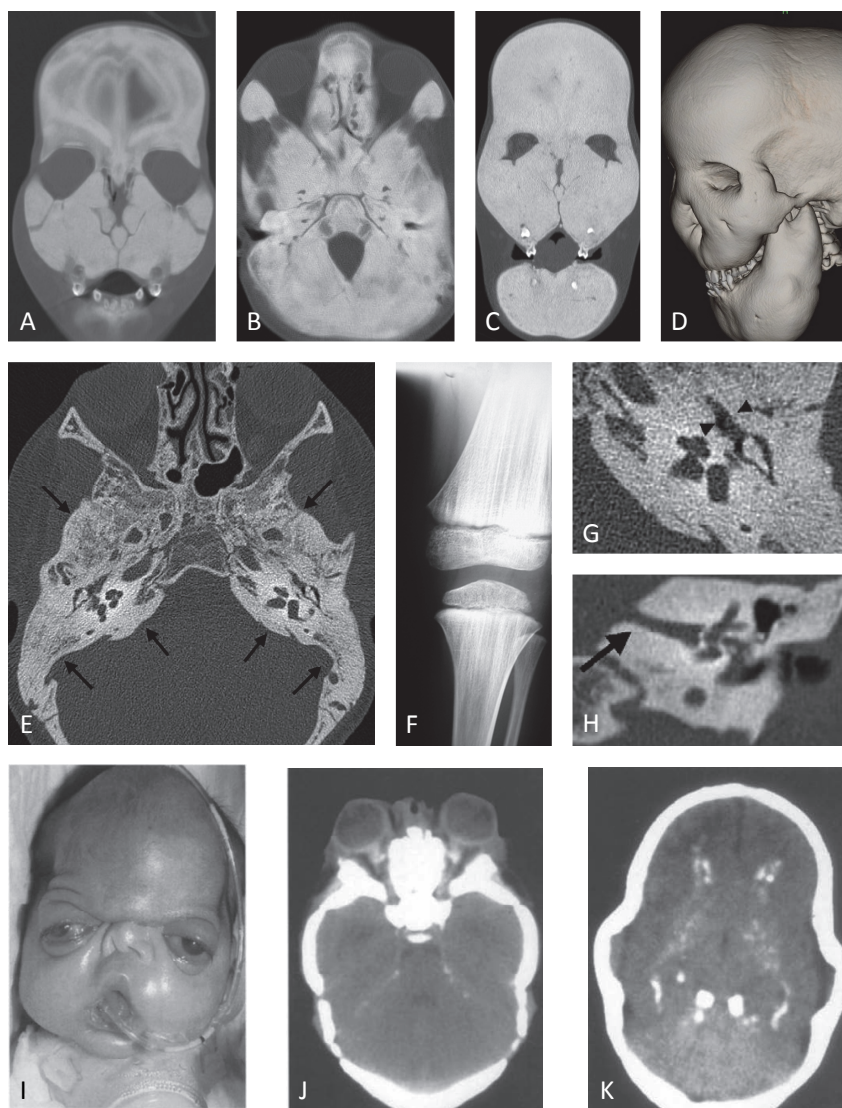


Figure 2.9 Disorders with increased bone formation (2). A-D: **Craniodiaphyseal disease**. A and B: Coronal and axial CT of 20-month-old child. Extreme hyperostosis of the facial bones, the calvaria and the skull base. C and D: coronal CT and 3D-reconstruction of the same child at 9 years. E-H: **Osteopathia striata with cranial stenosis**. E: Axial CT of an adult patient. There is moderate hyperostosis at the level of the skull base (arrows). In this patient, the visualised neuroforamina are patent. F: AP Radiograph of femur. Pathognomonic longitudinal striations. G: Detailed view of a left axial temporal bone with soft tissues in the middle ear due to Eustachian tube encroachment. H: Coronal reconstruction of left temporal bone (same patient as G) demonstrating a patent internal auditory canal (arrow)¹⁰⁹. I-K: **Raine syndrome**. I: Typical phenotype with proptosis, depressed nasal bridge, bowed upper lip and micrognathia. J: marked calvarial and anterior skull base hyperostosis with bilateral choanal obstruction, proptosis. K: Typical periventricular calcifications¹²².

4. Conditions with exclusive skull involvement

Hyperostosis cranialis interna

HCI is a disorder with an autosomal dominant transmission pattern so far only described in 15 cases in the Netherlands^{126,127}. The disorder is characterised by progressive hyperostosis and osteosclerosis of the skull base as well as the calvaria (Figure 2.10A-B). The calvaria and skull base display typical irregular endosteal hyperostosis. The diploë is not obliterated and hyperostosis seems to be less dense than normal cortical bone.

The disorder generally becomes symptomatologic in childhood or adulthood, whereas the first radiologic abnormalities are generally seen late in the first decade¹²⁸. The disease is slowly progressive, however hyperostosis generally settles down after the fourth decade. Women tend to be more severely affected. Most frequently the first symptoms derive from internal auditory canal encroachment. Facial nerve palsy is the most common symptom patients address to the physician with. Prior to this, vestibulocochlear nerve dysfunction might be present subclinically¹²⁹. Later on, olfactory, optic, and trigeminal nerve dysfunctions are seen, also due to encroachment of the corresponding neuroforamina. Also, headache and potentially eventually elevated intracranial pressure can occur due to decreased intracranial volume. Patients develop mandibular exostoses facing intra-orally without clinical consequences. The facial bones and tubular bones are not affected. The facial appearance is normal.

LRP4, *LRP5*, *SOST* and *TGFB1* are excluded as causative genes based on linkage studies and mutation analysis, and the region of the causative gene has been delineated: 8p21¹³⁰.

Hyperostosis frontalis interna

Hyperostosis frontalis interna (HFI) is not a genetic bone dysplasia, not even a disease (Figure 2.10C-D). However it is listed in this review, because it is important for clinicians to know about the innocence of HFI to avoid unnecessary diagnostics and even treatment.

In contemporary medical history it is mostly described as a coincidental finding, in up to 5-12% of the general population (varying degrees), so it cannot be denied. It is mentioned here because to some extent it mimics hyperostosis cranialis interna or other disorders. It is defined as bony overgrowth of the internal table of the frontal bone in various degrees, ranging from isolated, elevated bony islands to continuous bony overgrowth involving more than 50% of the frontal endocranial surface¹³¹. In the vast majority of cases it is an asymptomatic condition. In the anatomical, anthropological and forensic literature HFI is discussed as well. Cadaver studies demonstrate that HFI is present in a considerable number of ancient skulls¹³¹⁻¹³³.

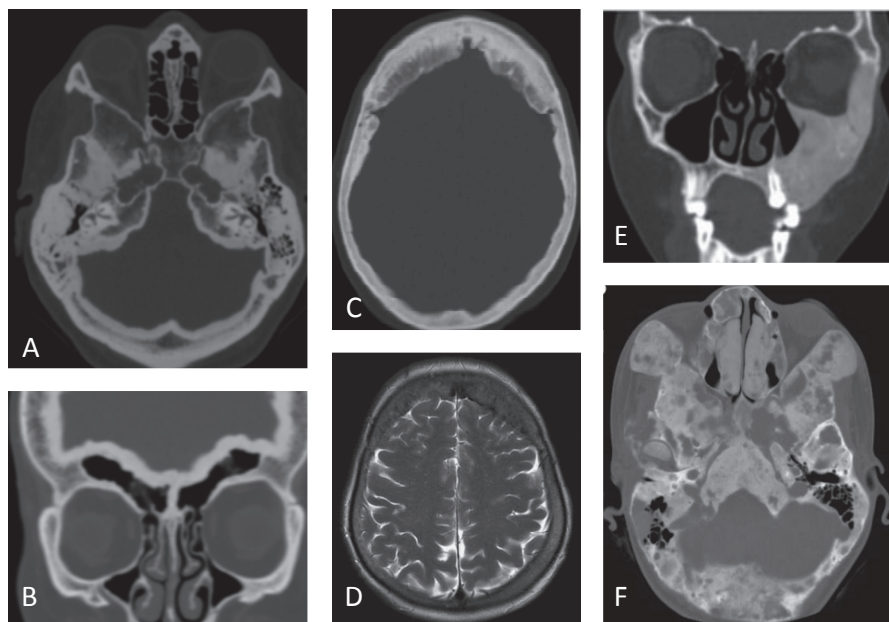


Figure 2.10 Disorders with exclusive skull involvement, fibrous dysplasia and McCune Albright syndrome. A: Axial CT image of an adult patient with **hyperostosis cranialis interna**. Hyperostosis of the endosteal layer of calvarial bone (images of own collection) B: Coronal CT reconstruction in a patient with hyperostosis cranialis interna at the level of the frontal sinuses and orbitae. Note the sparing of the facial bones, the diploë and the outer cortex of the calvaria. C and D: Axial CT and T2-weighted MR images of patients with **hyperostosis frontalis interna**. Incidental findings. E: An 11-year-old female with monostotic **fibrous dysplasia** of the left zygomatic-maxillary region. Ground-glass aspect¹⁵¹. F: Axial CT at the level of the skull base in a patient with **McCune Albright Syndrome**¹⁵². Fibrous dysplasia (FD) and McCune Albright Syndrome (MAS) are mentioned separately because, unlike the other disorders, it is not purely a bone dysplasia and there is no familial occurrence. It is reviewed and illustrated because craniofacial involvement is very common in FD and MAS. It is due to a postzygotic mutation in the guanine nucleotide stimulatory protein (GNAS1) gene at a very early stage of embryonic development. Cells carrying the mutation (mosaicism) can be present in endocrine glands, skin, or bone tissue. The mutation leads to hyperfunction of skeletal progenitor cells and abnormal osteoblasts. Bone is replaced by fibrous connective tissue and poorly formed trabecular bone. Patients almost always become symptomatic before the age of 30 and disease progression tends to slow down in the course of life. In case of monostotic lesions (75-80%) it is called FD, in case of polyostotic lesions it is called MAS (20-25%). Craniofacial involvement is reported in over 90% in patients with MAS. In FD the zygomatic-maxillary complex and the proximal femur are the most commonly involved sites. Monostotic lesions are obviously easy to differentiate from other – symmetrical – skeletal dysplasias. Polyostotic craniofacial lesions can be so generalised that the whole skull base is affected. Radiologically affected bone has ground glass appearance. Craniofacial symptoms – depending on the location – can be visual impairment, hearing loss (due to ossicle fixation or internal auditory canal narrowing), facial deformity, nasal obstruction, pain and dental malocclusion¹⁵¹. Treatment of craniofacial symptoms is generally surgical.

Sporadically it has been published in case reports to be associated with neurological/cognitive dysfunction^{134,135}, endocrinopathies including obesity or hirsutism¹³⁶ but the significance of these findings is doubtful. It is postulated that cognitive function is caused by frontal dysfunction by pressure of the bony masses¹³⁷. If HFI is accompanied with a combination of neuropsychiatric symptoms, persistent headache, obesity and endocrinopathies, it is also called the Morgagni-Stewart-Morel syndrome¹³⁸. Again, a causative relationship between the different abnormalities has never been demonstrated.

X-linked calvarial hyperostosis

In 1986 Pagon et al. described a family with an X-linked recessive disorder characterised by isolated calvarial thickening. Symptoms were prominent frontoparietal bones, flat nasal root and short upturned nose, frontal bossing with ridging of the metopic and sagittal sutures, and lateral frontal prominences. The mandible was normal, as were the clavicles, pelvis and long bones. The thickened bone in the skull appeared to be softer than normal bone. Histological examination of the hyperostotic calvarial bone and a bone marrow biopsy showed dense trabecular bone separated by stroma packed with large, morphologically unusual histiocytes.

The transmission pattern seems to be X-linked recessive. Female carriers show no clinical symptoms. Despite calvarial hyperostosis, increased intracranial pressure and cranial nerve entrapment did not occur. The major disability appears to be cosmetic¹³⁹. To date, this is the only family that has been described with X-linked calvarial hyperostosis. A causal gene has not yet been found. Recently the gene has been localised to a small region on chromosome Xq27.3-Xqter¹⁴⁰.

Discussion / conclusion

Sclerosing bone dysplasias have long been categorised with the emphasis on phenotypic and radiologic characteristics. Along with the detection of dozens of genetic underlying causes of the different disorders and with the upcoming clinical availability of genetic analysis, gradually a shift is seen towards division into genetic cause of the disease. However, it should not be forgotten that a patient initially presents with a symptom, not a diagnosis. It is therefore important that not only geneticists, but also clinicians should be aware of different bone dysplasias. Although we are about to enter an era of diagnostic whole-genome sequencing, the clinical symptoms and radiologic characteristics should be easily accessible to facilitate the diagnosis.

A definite clinical diagnosis remains challenging especially if the (radiological) symptoms are subtle in children and mildly affected individuals. Patients often address a specialist in the field corresponding with symptoms, e.g. otolaryngologist, neurologist or orthopaedic surgeon. However, if a (genetic) bone dysplasia is suspected, complete

skeletal survey should be performed, preferably coordinated by a paediatrician or bone specialist. Family history is important, also in case consanguinity is suspected. A clinical geneticist is of crucial value, in the first place if the diagnosis is uncertain and – later on – in case there are questions about heredity.

Making a correct diagnosis has been proven to be difficult in many cases. For many disorders, the number of published cases is very limited. Furthermore, in many diseases there is a clinical and radiological overlap which makes it even harder to make a correct diagnosis. Table 2.3 can be a guideline in making a correct diagnosis based on clinical and radiological findings. Once a presumed diagnosis is made, genetic and molecular analysis should be performed to confirm the diagnosis, especially if there is a recurrence risk or if treatment issues (e.g. in case of osteopetrosis) are under consideration¹⁴¹.

Also, important pathways in bone metabolism, such as the WNT, TGF β and NF κ B pathways are now better understood. This allows comparison of different disorders with respect to these mechanisms.

Although many genes and pathways involved in bone metabolism are already known, there are still many rare bone dysplasias where the responsible gene is unknown. Identification of such genes may lead to important information to further unravel the complex process of bone homeostasis.

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Table 2.3 Checklist of bone dysplasias for diagnostic work-up purposes.

	Autosomal recessive osteopetroses	Autosomal dominant osteopetrosis	Dysosteosclerosis	Pycnodysostosis	Cranio-metaphyseal disease	Paget's disease of bone	Juvenile Paget's	High Bone Mass phenotype	Van Buchem disease	Sclerosteosis	Camurati-Engelmann disease	Osteopathia striata with cranial stenosis	Cranio-diaphyseal dysplasia	Raine syndrome	Hypertostosis cranialis interna	Hypertostosis frontalis interna	X-linked calvarial hyperostosis	Fibrous dysplasia and McCune Albright syndrome
Disease course																		
(Bone) Abnormalities at birth or first year	✓	±	±	✓	✓	×	×	×	✓	×	×	✓	✓	✓	×	×	✓	±
(Bone) Abnormalities in childhood	✓	✓	✓	✓	✓	×	×	×	✓	✓	✓	✓	✓	✓	×	×	✓	✓
Bone abnormalities																		
Asymmetric/unilateral	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	✓
Facial dysmorphism due to hyperostosis	×	×	×	×	✓	±	±	×	✓ ¹	✓ ¹	×	✓	✓	✓ ^{4,5,6}	×	×	✓	±
Craniofacial structural abnormalities (apart from hyperostosis/osteosclerosis)	×	×	×	✓ ^{2,3,4}	✓	×	×	± ³	×	×	×	✓ ⁵	×	×	×	×	×	×
Elevated (bone-related) serum markers	✓	✓ ⁷	×	×	×	±	✓	×	✓	✓	✓	×	✓	×	×	×	×	±
Tendency to fractures	✓	±	✓	✓	×	✓	✓	×	×	×	×	×	×	×	×	×	×	± ⁸
Stature	=	=	>	<	=	=	>	=	<	>	=	=/≤	=/≤	>	=	=	=	=
Non-osseous abnormalities																		
Stigmata	×	×	± ⁹	✓ ¹⁰	×	×	×	×	×	✓ ^{11,12}	×	✓ ^{13,14}	×	×	×	×	×	✓ ¹⁵
Anaemia due to bone marrow displacement	✓	±	±	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Dental abnormalities/problems	±	±	✓	✓	✓	±	×	±	×	×	×	±	±	✓	×	×	×	±
Neurological impairment																		
Cranial nerve dysfunction	16																	
Visual impairment	✓	±	✓	×	✓	×	×	×	±	±	±	×	✓	×	×	×	×	±
Facial nerve	✓	±	×	×	✓	×	×	×	✓	✓	±	±	✓	×	×	×	×	±
Vestibulocochlear nerve ^{6*}	✓ ^{6*}	± ^{6*}	± ^{6*}	×	✓ ^{6*}	± ^{6*}	✓ ^{6*}	×	✓ ^{6*}	✓ ^{6*}	± ^{6*}	± ^{6*}	✓	✓	±	×	×	± ^{6*}
Arnold Chiari malformation	±	×	×	×	±	×	×	×	×	×	±	×	±	×	×	×	×	×
Hydrocephalus/increased intracranial pressure	±	×	×	×	±	×	×	×	±	✓	±	×	✓	×	×	×	×	×
Disease-related developmental delay	×	×	±	×	± ¹⁷	×	✓	×	×	×	×	±	✓	✓	×	×	×	×

✓ = (almost) always present, ± = never present, 1: mandibular overgrowth, 2: craniosynostosis possible, 3: obtuse mandibular angle, 4: wide cranial sutures, 5: Pierre Robin sequence, 6: low-set ears, 7: increased tartrate-resistant acid phosphate¹³, 8: pathologic fracture possible in case of McCune Albright syndrome, 9: skin patches (pachy red-violet spots), 10: brachydactyly, 11: syndactyly, 12: brachydactyly, 13: congenital cardiac and gastrointestinal anomalies, 14: hypertelorism, 15: café-au-lait spots and endocrinopathies in case of McCune Albright syndrome, 16: narrowed jugular foramen described, 17: autosomal recessive form, § sensorineural hearing loss, * conductive hearing loss, < short stature, > tall stature, = normal stature.

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Part II

**Clinical, radiological and metabolic features of
hyperostosis cranialis interna**

Chapter 3

Phenotypic manifestations and management of hyperostosis cranialis interna

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Abstract

Hyperostosis cranialis interna is a hereditary bone disorder that is characterised by endosteal hyperostosis and osteosclerosis of the calvaria and the skull base (OMIM 144755). The progressive bone overgrowth causes entrapment and dysfunction of cranial nerves I, II, V, VII and VIII, its first symptoms often presenting during the first two decades. This study analyses the clinical course of 13 affected individuals of three related subfamilies (32 individuals). The disorder has an autosomal dominant transmission pattern. Facial and vestibulocochlear nerve dysfunction are most frequently reported. Surgical decompression of the impaired cranial nerves is advised in the early symptomatic period or even in the presymptomatic period in high-risk individuals.

Introduction

Hyperostosis cranialis interna (HCI) is a hereditary disorder that is characterised by endosteal hyperostosis and osteosclerosis of the calvaria and the skull base (OMIM 144755), first described by Manni et al.¹. The progressive bone overgrowth causes entrapment and dysfunction of cranial nerves I, II, V, VII and VIII. There is resemblance with sclerosteosis and Van Buchem disease, especially the endosteal aspect of the hyperostosis²⁻⁴. Individuals with Camurati-Engelmann disease present with similar (endosteal) cranial abnormalities, however most patients have predominant radiological skeletal abnormalities^{5,6}. There are some striking similarities to hyperostosis frontalis interna (HFI). HFI comprises benign isolated frontal endosteal hyperostosis with the same pattern as HCI^{7,8}. In HCI the viscerocranium and the tubular bones are explicitly not involved. The facial appearance is normal. Within the international classification of genetic skeletal disorders HCI matches in the group of disorders with increased bone density with metaphyseal and/or diaphyseal involvement⁹.

In this study we describe three related subfamilies with common progenitors affected with HCI to analyse the course of the disorder. The older generations were initially investigated in 1985¹. The interval between both studies may give insight in the initiation and the evolution of the disease and may create basic principles to facilitate decisions in counselling and interventions concerning the affected patients.

Materials and methods

The medical history was recorded through a standardised checklist. Examination was performed by two doctors. Neuro-otological examination included a routine ENT-examination with special attention to skull and facial abnormalities and evaluation of the cranial nerve functions. Smell and taste were tested bilaterally using Sniffin' sticks¹⁰. Balance was tested clinically using Unterberger, Romberg and head impulse tests. The morphology of the face and the head was photographed. Patients were inspected for other skeletal anomalies.

Pure tone and speech audiometry were obtained. The results are reported as pure tone average (PTA), the average of thresholds at 1, 2 and 4 kHz. Acoustic impedance and stapedial muscle reflexes were measured as well as click-evoked otoacoustic emissions and auditory brainstem responses.

Vestibular examination comprised oculomotor function assessment and electro-nystagmography by caloric and rotational chair provocation. In this paper, the general results of tone audiometry and vestibular examination are reported; a detailed report of audiological and vestibular data will appear in a separate article.

Visual acuity, manifest refraction, colour vision and pupillary reaction were examined by the same ophthalmologist and fundoscopy was performed. Additionally, orthoptic evaluation (including eye movements) and perimetric tests were performed. The intra-ocular pressure was measured by an applanation tonometer. If indicated, an ultrasonogram of the optic nerve was made.

All examined patients underwent computed tomography scanning. In this paper, radiological data are only used to confirm or exclude HCl and to assess radiological progression. Details of radiological imaging will appear in a separate article.

Three related Dutch families, comprising 32 related individuals, have common progenitors (Figure 3.1), three deceased. The first known affected individual was born in 1904. Information regarding her was obtained through her children. Nine of 11 affected individuals who were investigated in 1985 have been investigated again in this study (two deceased). In the present study, a total of 22 individuals have been examined, of 28 living family members. Six children were not examined yet because the parents considered them being too young (all under the age of four); there was no history of complaints related to HCl. There was no consanguinity between spouses.

An individual without radiographic abnormalities is considered unaffected when the age of 18 is reached. Twelve individuals (without abnormalities) have not yet reached this age.

Results and clinical reports

In total 13 individuals are radiologically affected, 2 of them are asymptomatic. Six family members are definitively unaffected.

The case reports of affected individuals will be described per family. We mainly focus on abnormal symptoms and findings. Individuals are given a case number, consisting of a Roman number (generation) and an Arabic number, corresponding with the pedigree (Figure 3.1). If possible the actual symptoms are compared to those in 1985 as well as the degree of radiological progression. The chronology and the severity of their symptoms can easily be traced in Figure 3.2 and Table 3.1.

The first known affected common family member (individual I.1), born in 1904, was the great-great-grandmother of the youngest generation. She was known to have a right facial palsy since she was 19. She had frequent severe headaches, impaired vision and impaired smell. She died at the age of 39.

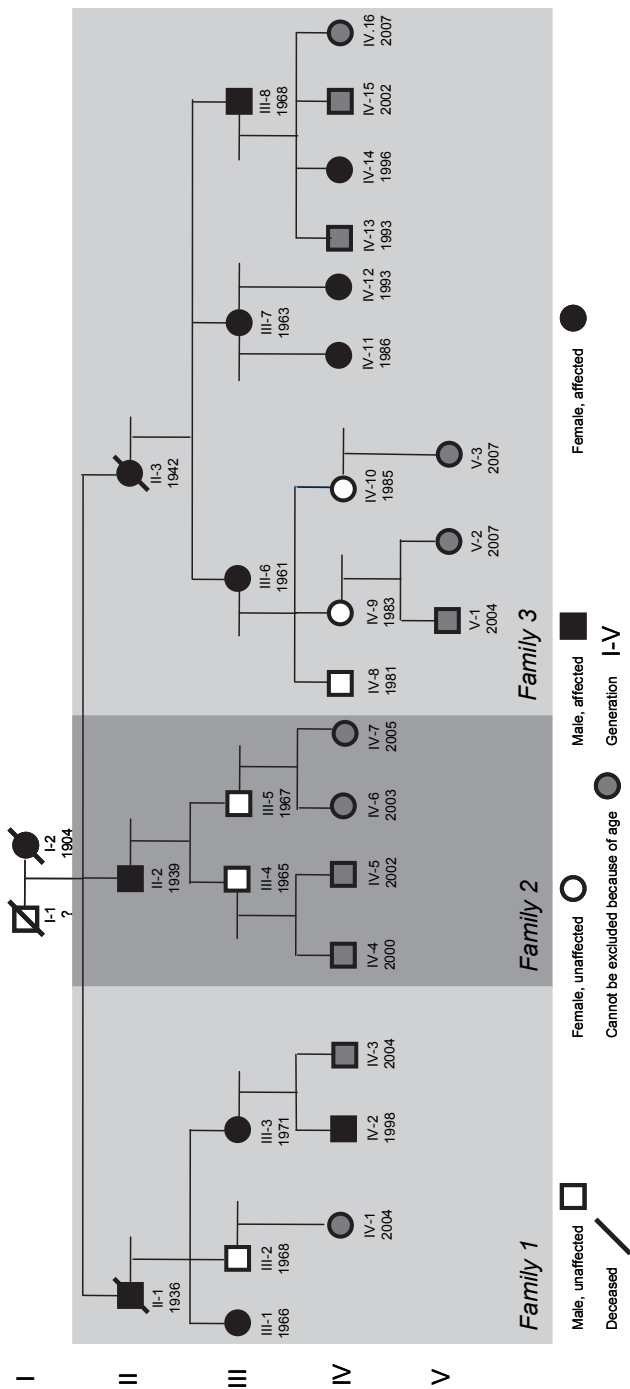


Figure 3.1 Hyperostosis cranialis interna: pedigree of the affected individuals over five generations.

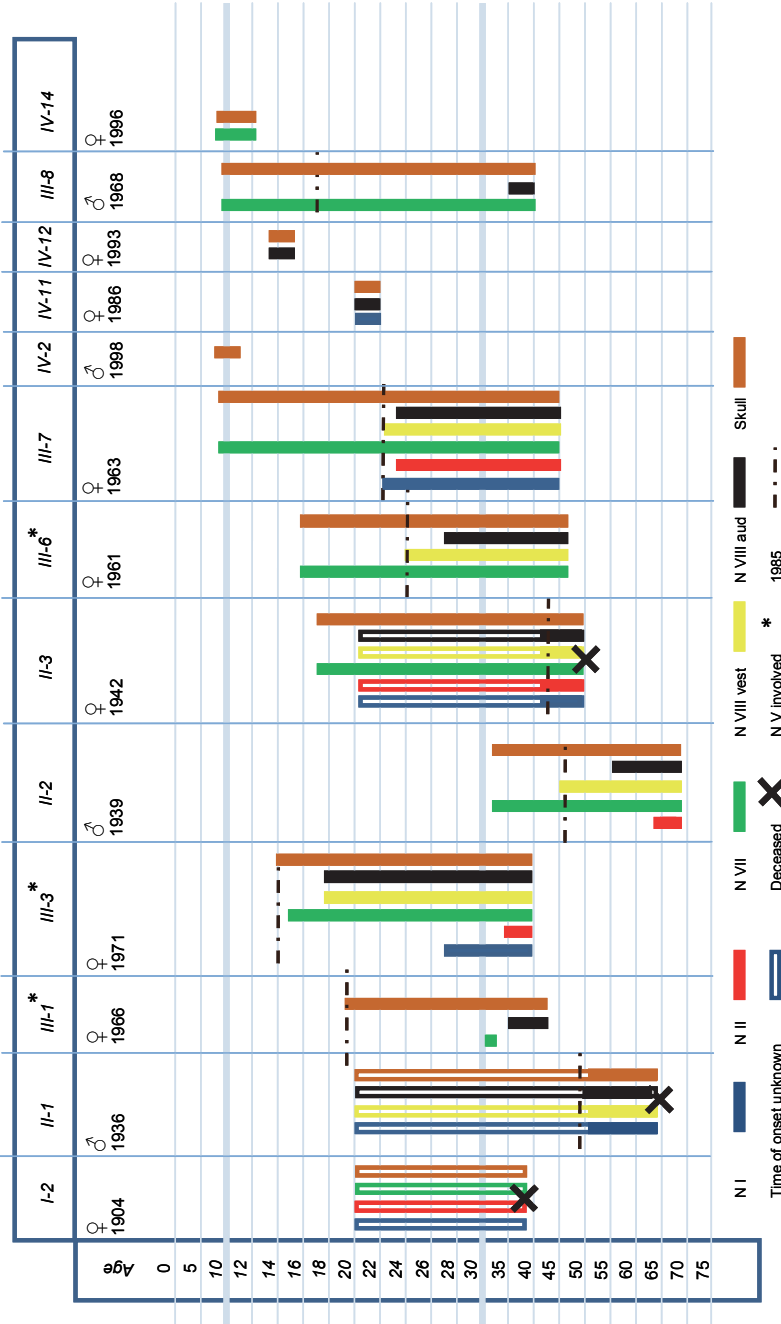


Figure 3.2 Chronology of symptomatology. In the vertical axis the patient's age. Seven of the patients have been examined both in 1985 [Manni et al., 1990] as well as in 2007. Asymptomatic skull abnormalities were then detected (e.g. III.1, III.5). Conversely, in other individuals the initiation of the skull abnormalities is depicted as if it started simultaneously with the first symptom, since the exact onset is unknown (e.g. IV.12, II.3).

Table 3.1 Overview of the symptom complex of the living affected individuals.

Patient	Sex	Age	NI	NII	NV	NVII Onset (age)	NVII Present HB	NVIII Onset	Sensorineural hearing loss (dB) 1985	NVIIV	Headaches Onset	Remarks
10-20	IV.14	F	13	-	-	L:8 R:9	2 1	-	Unborn	-	-	Bilateral facial nerve decompression
10-20	IV.12	F	16	-	-	-	-	L: <20 R: <20	Unborn	5-10 10-20	<20	
20-30	IV.11	F	23	R: <20	-	-	-	L: <20 R: <20	Unborn	5-10 5-10	-	
30-40	III.3	F	38	L: <30 R: <40	papil- oedema	L:CT R:19	1 3	L: <30 R: <30	-	10-20 20-30	<40	Bilateral hypofunction
40-50	III.8	M	41	-	-	L:9 R:13	3 1	L: <30 R: <30	-	20-30 5-10	<40	?
30-40	III.5	M	42	-	-	-	-	-	-	-	-	Only radiographic abnormalities
30-40	III.1	F	43	?	-	L:31 R:CT	1 1	L: <40 R: <40	10-20 10-20	30-40 20-30	<40	Clinical suspicion of right hypofunction
40-50	III.7	F	46	<40	L:Blind R: -	L:11 R:9	4 4	L: <30 R: <30	30-40 70-80	Deaf Deaf	<40	Auditory brainstem implant, optic nerve decompression left Ocular hypertension
40-50	III.6	F	48	-	R: 42	L:14 R:CT	3 1	L: <40 R: <40	-	20-30 20-30	-	Clinical suspicion of left hypofunction
60-70	II.2	M	70	-	-	L:33 R:33	2 1	L: <40 R: <40	-	50-60 10-20	-	Infectious ear pathology left, CRM

HB: House-Brackmann scale; sensorineural hearing loss: average perceptible threshold at 1,2 and 4 kHz (dB); CT: chorda tympani; nNVIIa: auditory nerve; NVIIv: vestibular nerve; CRM: conservative radical mastoidectomy.

Family 1

Individual II.1, ♂ 1936. This person was moderately affected. Since childhood there had been chronic otitis media. In 1985 he had left-sided olfactory impairment, moderate bilateral sensorineural and conductive hearing loss (the latter due to middle ear surgery) and bilateral diminished vestibular function¹. There was explicitly no history of facial nerve involvement. CT scanning revealed extensive hyperostosis and sclerosis of the calvaria and the skull base. The disease has remained clinically stable until his death at the age of 69 (unrelated to HCI).

Individual III.1♀, 1966. At the age of 19 (1985), she had asymptomatic radiological skull abnormalities¹. Ever since, there have been remarkable clinical and radiological progression. This individual is now severely affected. At the age of 31, she had a complete left facial nerve palsy during one week, which recovered completely. In her mid 30s she developed severe right-sided trigeminal neuralgia (all branches). She underwent a foramen magnum decompression at the age of 40 in another hospital because of a Chiari I malformation with concurrent headache, nausea and swallowing difficulties since 1 year. Her complaints resolved for only 1 year. After the operation she developed a feeling of disequilibrium and staggering gait without vertigo. Recently the trigeminal neuralgia increased despite percutaneous Gasser ganglion blockage and radiofrequency treatment. On current physical examination there is anosmia (Figure 3.3F), bilateral anaesthesia of the tongue and normal facial sensibility. Facial mimic function is intact. Audiometry reveals bilateral sensorineural hearing loss (PTA 30dB). Vestibular function on clinical evaluation is diminished on the right side. Ophthalmologic assessment is normal.

Individual III.3, ♀ 1971 (Figure 3.3B and 3.3C). She was examined in 1985 and had asymptomatic radiological skull abnormalities¹. There has been fairly rapid radiological progression since then as opposed to moderate clinical progression. The radiological abnormalities are now extensive. At the age of 15 she developed a sudden facial paralysis at the right side. With conservative treatment her facial nerve function recovered to House-Brackmann (HB) grade III in half a year. During her first pregnancy (age 27) she developed total anosmia, which recovered thereafter and again she lost her sense of smell during her second pregnancy. Sporadically, there is temporary hyposmia. Hearing at the right side is worse and is accompanied with continuous tinnitus since 7 years. She experiences severe headaches, especially during menstruation. Upon current examination senses of smell and taste are completely lost bilaterally. Left trigeminal sensible function is absent in all branches without a history of neuralgia. There is a right facial nerve palsy HB grade III. Audiometry reveals mild sensorineural hearing loss (PTA of 25 and 15 dB, respectively). There is bilateral hyporeflexia of the vestibular apparatus. Ophthalmologic examination reveals right-sided asymptomatic papilloedema on fundoscopy as well as ultrasonography.

Individual IV.2, ♂ 1998. This individual is asymptomatic, but the CT scan reveals subtle sclerotic changes in the skull base suggesting HCI.

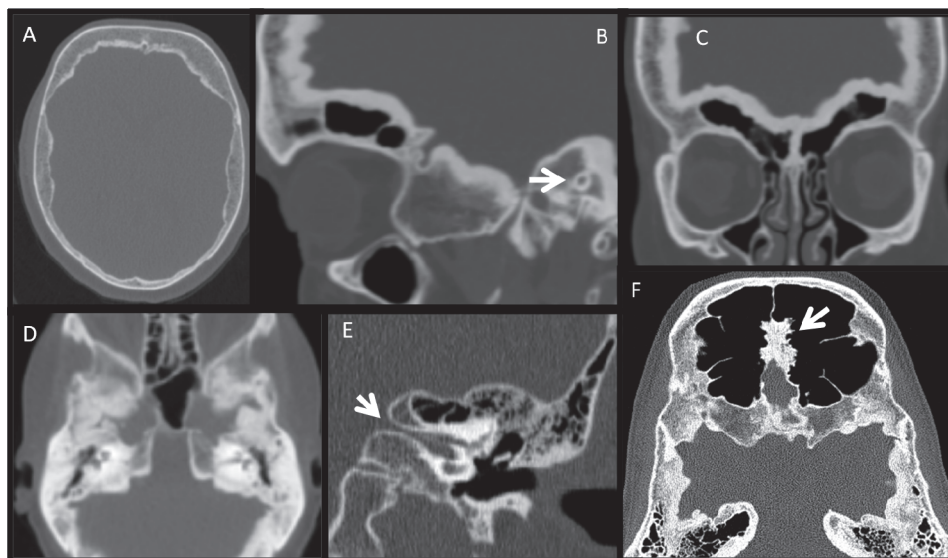


Figure 3.3 CT-imaging. A: Axial image of III.8. Note the frontal and parietal bones are affected. Note the diploë is not obliterated. B and C: Sagittal and coronal reconstructions of III.3. Evident endosteal apposition of bone at the base of skull, whereas the facial bones are unaffected. Arrow: narrowed internal auditory canal. D: Axial image of III.6. Typically the region of the greater wing of the sphenoid bone and the squama temporalis are most severely affected. E: Narrowing of the internal auditory canal due to endosteal apposition (arrow) in IV.14. F: Axial image of the anterior and middle fossa of III.1. Arrow: osteosclerosis of the olfactory region.

Family 2

Individual II.2, ♂ 1939. In this individual, there is late and mild onset of the disease. Although in 1985 obvious radiological abnormalities were present, there were only moderate symptoms. Since then symptoms have stayed relatively stable. At the age of 32 this individual had intermittent facial nerve impairment at the right side. There was no recurrence of sudden palsies after this event. In the course of his life, he suffered from progressive headaches. He underwent a conservative radical mastoidectomy for chronic mastoiditis at the left side (not related to bony encroachment of the Eustachian tube). In 1985¹, there was bilateral diminished function of both labyrinths. Currently, he experiences continuous tinnitus at the right side. On current physical examination, there is a residual left facial nerve palsy (HB II). There is bilateral epiphora and no sense of taste. Audiometry reveals mixed bilateral hearing loss (PTA 70 dB at the left, 45 dB at the right, air-bone gap 25 dB). Ophthalmologic assessment reveals diffuse loss of peripheral visual acuity.

Family 3

Individual II.3, ♀ 1942. This individual has deceased and was severely affected. At the age of 18 she developed a left facial nerve palsy, which recovered and recurred 3 years later. She was examined in 1985 at the age of 43¹. Then, there was anosmia, she had bilateral proptosis, central scotomas, bilateral optic atrophy and hence absence of visual evoked potentials. Her left facial nerve function revealed synkineses (HB II) and she had left ageusia. She was deaf at the left side and had moderate sensorineural hearing loss at the right side. Vestibular function was absent at the left and diminished at the right side. She deceased after a diagnostic lumbar puncture at the age of 55, due to brainstem herniation. In the last months of her life she was increasingly somnolent and even subcomatose during her last days with concurrent headaches. There were no other symptoms of increased intracranial pressure such as papilloedema or focal neurological signs.

Individual III.6, ♀ 1961 (Figure 3.3D). This individual had moderate clinical symptoms and moderate radiological skull abnormalities in 1985. Although radiological progression is evident since then, symptomatology has remained relatively stable. She presented with left facial nerve paralysis at the age of 16 and right facial nerve paralysis at the age of 20. The left facial nerve function recovered within 6 months to HB grade III with conservative treatment, the right function completely recovered, except for the taste function. In 1985¹, at the age of 22, there was bilateral vestibular hyporeflexia. Three years later, there was a sudden sensorineural hearing loss at the left side, accompanied with an episode of vertigo. The hearing recovered after conservative treatment. At present, she has bilateral stabbing ocular pain, frequent headaches and episodes of right trigeminal neuralgia. She has episodes of paroxysmal vertigo with full aural feeling and hyperacusis at the left side. She experiences progressive bilateral hearing loss since 10 years and bilateral tinnitus. On physical examination, there is right-sided hypesthesia in the first and third trigeminal branches. There is a left HB grade III facial nerve palsy; the sense of taste is completely lost bilaterally. Clinical vestibular examination reveals residual function of the left labyrinth. There is mild symmetric sensorineural hearing loss (PTA 20 dB). There is a frontal exostosis. Ophthalmologic examination reveals ocular hypertension.

Individual III.7, ♀ 1963. This individual had extensive radiological abnormalities in 1985 along with severe symptoms. Recent CT scanning reveals progressive radiological abnormalities. The severity of symptoms has proceeded as well. She developed a right facial nerve paralysis when she was 9 and a left paralysis when she was 11. At the age of 23, during her first pregnancy, she suddenly became deaf at the right side (1985)¹. This did not recover under steroid therapy. There was also right vestibular areflexia. One year later, she developed mild left-sided sensorineural hearing loss, responding under steroid therapy. Her left ear became deaf at the age of 36. At that time, she had total anosmia and right-sided opticopathy with impaired vision. She underwent a right-sided optic nerve decompression because of further visual deterioration (age 38).

Visual acuity was reduced to light perception, which did not change after the procedure. At the age of 44 an auditory brainstem implant was placed at the left side, with very good auditory results. At present, she has severe headaches and stabbing facial pains and visible facial dystonias. Recent physical examination reveals total anosmia and ageusia. The facial nerve function is grade IV/VI at both sides. Clinical vestibular examination suggests residual function of the left vestibular apparatus. Ophthalmologic investigation has not changed.

Individual IV.11, ♀ 1986. Her medical history is uneventful, her complaint is hearing deterioration. Physical examination reveals the inability of smell discrimination at the right side. Audiometry reveals mild symmetric sensorineural hearing loss (PTA 8dB). Radiological imaging confirms HCl.

Individual IV.12, ♀ 1993. Experiences frequent progressive mild headaches, but has no other complaints. On physical examination, no abnormalities are found. Audiometry reveals mild asymmetric sensorineural hearing loss (PTA 8dB at the left and 13dB at the right side). Radiological imaging confirms HCl.

Individual III.8, ♂ 1968 (Figure 3.3A). In 1985 there were mild symptoms along with moderate radiological abnormalities. Although there is some radiological progression, his symptoms have remained relatively stable. He had facial paralyses at the age of 9 (left) and 13 (right). Moreover, he suffers from recurrent headaches. Hearing is worse at the left side since the age of 30 along with continuous tinnitus. Recent examination reveals symmetric exostoses of the anterior wall of the external acoustic meatus and exostoses of the left frontal bone and the mandible at the left side. Facial nerve function is HB grade I and III at right and left side, respectively. Taste function is impaired at the left side. Audiometry reveals mild left-sided sensorineural hearing loss (PTA 20dB). Apart from amblyopia, no other abnormalities on ophthalmologic examination are found.

Individual IV.14, ♀ 1996. This individual developed sudden facial paralysis at the age of 8 and 9. Both sides responded only partially to steroid therapy (right side HB IV, left side HB III). Bilateral facial nerve decompression via middle fossa approach with one year interval were performed in our institute. Only the intrameatal part of the facial nerve was compressed (Figure 3.3E). Facial nerve function recovered within one year to HB I at the right and HB II at the left side. She experiences continuous bilateral tinnitus. Audiometry reveals normal hearing levels.

Facial nerve

In total 9 individuals have had fifteen facial nerve palsies. Facial nerve impairment also was their first symptom. It occurred between 8 and 30 years of age in females (n=7) and between 9 and 33 years of age (n=2) in males. In only 3 patients the facial nerve impairment occurred unilaterally (II.2, III.1 and III.3). Typically, there is a rapidly evolving initial paralysis, followed by a partial and sometimes complete recovery under steroid therapy (Figure 3.4). Mimic function recovered to HB grade I in 4 of the palsies

and to HB grade II in 3 of the palsies after conservative treatment. In the remaining 5 palsies facial nerve function recovered to HB grade III or IV, with severe synkineses. None of the subjects experienced delayed deterioration of mimic function after stabilisation of the facial nerve function, despite progressive intrameatal encroachment according to radiological data. Facial nerve decompression via middle fossa approach by opening the internal auditory canal has been performed bilaterally in one patient (IV.14) at the age of 9 with good outcome. Outcome of taste function is much poorer: it recovered bilaterally in the individual in which surgical decompression was performed but remained absent in all other individuals. Three individuals have unilateral taste impairment without a history homolateral facial palsy.

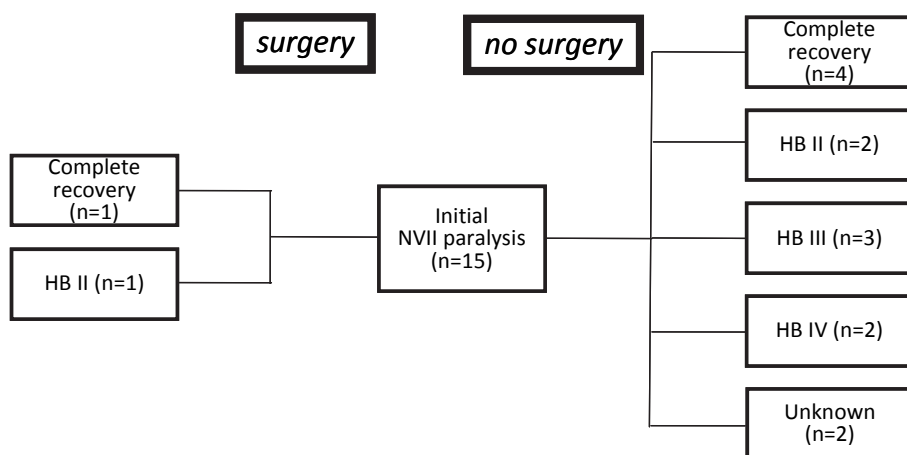


Figure 3.4 Evolution of the 15 facial nerve palsies among 9 patients.

Vestibulocochlear nerve

Ten individuals have confirmed vestibulocochlear nerve dysfunction. Six of them have vestibular dysfunction. The onset of vestibulocochlear nerve impairment can be slumbering, characterised by tinnitus, sensorineural hearing loss and increasing balance problems. In some individuals the onset was subclinical. On the other hand, four individuals had a sudden sensorineural hearing loss, all female and all linked to hormonal events, such as pregnancy, oral contraceptive use and ovulation. None of the patients have HCI-related conductive hearing loss. There are two patients with a history of sudden vestibular nerve impairment (III.6, III.7), both during a sudden sensorineural hearing loss event but without simultaneous facial nerve symptoms. In two patients there has been a slowly progressive vestibular function decrease (II.2 and III.3), characterised by the absence of vertiginous symptoms.

Other symptoms

The loss of the sense of smell is registered in six patients. The onset is generally in the third decade, either subclinical, or linked to hormonal changes.

Ocular symptoms occur later in life (n=5). Ocular hypertension is seen in one patient and is not supposed to be HCI-related.

Trigeminal impairment is reported in three patients and consists of facial and tongue numbness or severe trigeminal neuralgia. It can occur in separate branches of the nerve suggesting impingement at the level of the corresponding foramen or the nerve as a whole suggesting proximal encroachment.

The most severely affected patients suffer from intermittent headaches (n=5). In none of the patients with available CT-scans hydrocephalus is seen. One of the family members (II.3) died after a lumbar puncture during diagnostic work-up for severe headaches.

Discussion

Transmission and gender pattern

The pedigree has been identified until the beginning of the 20th century, because the parents of individual I.1 could not be traced. Within the pedigree there exists explicitly no consanguinity, nevertheless this cannot be confirmed for previous generations. The transmission pattern is autosomal dominant. In total five male individuals and nine female individuals have been affected.

Clinical comparison of the affected individuals suggests different degrees of severity of the disease. The difference between male and female patients is most remarkable. Females are more severely affected than males. None of the three symptomatic male patients are experiencing severe symptoms. The three female patients under 20 have serious skull abnormalities and are symptomatic. The four middle-aged living female patients all have multiple cranial nerve deficits including total deafness, single-sided blindness and severe trigeminal neuralgia. The reason for this evident sex difference remains unclear, but we suppose a hormonal influence on bone metabolism may play a role. This sex-difference displays remarkable similarities compared to HFI, women being more often and more severely affected⁷. Temporary differences in female patients are also remarkable: ovulation and pregnancy are reported to impair the sense of smell temporarily in several cases, probably due to progesterone-induced tissue edema of the perineurium.

Onset of disease, different symptoms

First symptoms often present in adolescence, the median age being 14. Early symptoms are an ominous prognostic factor for severe progression of the disease. Figure 3.2 shows an overview of the course of the disease throughout life. Radiological skull abnormalities are found before they become symptomatic, mainly in the sphenoid wings and the frontal bones where hyperostosis can occur relatively harmless. Facial nerve involvement is the most frequent first symptom, occurring mainly in adolescence. This is followed by sensorineural hearing loss. These nerves are affected first because of the endosteal apposition of bone near the internal auditory canal, noticed from the age of 7.

It was demonstrated that the first audiological signs appear first as prolonged latencies on brainstem evoked auditory potentials¹¹. In some cases vestibulocochlear nerve function gradually deteriorates, in other patients there are events of sudden sensorineural hearing loss or vertigo. Like in facial nerve dysfunction, it is remarkable that progressive hyperostosis in the region of the porus of the internal auditory canal results in moderate non-progressive hearing loss only in several patients.

Olfactory nerve and trigeminal nerve dysfunction generally occur in the third and fourth decade due to progressive osteosclerosis of the anterior fossa. Opticopathy occurs in a late stage if at all, due to bony encroachment at the level of the optic canal.

Progression of the disease

Six of the patients have been examined both in 1985 as well as in 2007, which gives better insight in the course of the disease. The degree of progression of the clinical symptoms of the disorder throughout life plays a key role in the discussion and decision whether or not to intervene in certain cases. Clinical progression generally occurs until the age of 40. After the fourth decade, progressive cranial nerve dysfunction is uncommon in most and radiological progression is minimal. Nevertheless in severely affected cases, untimely death may occur due to decreased intracranial volume. If possible, operative cranial nerve decompression is advised in the early symptomatic period. It is assumed that the effect of an operation will last until the active hyperostosis is moderated.

In older patients, progressive headaches are often mentioned, a feeling of pressure in the head. Whether the exact pathogenesis is raised intracranial pressure due to diminished cerebrospinal fluid drainage or the direct compression of the brain by the thickened bone remains unclear. Besides, it is difficult to verify whether this symptom is disease-specific, especially since the patients are aware of their own disease, which is a psychological burden for many.

Apart from radiological progression, which is a measurable value, it appears that there are not many independent reliable clinical factors to predict the clinical course. Olfactory and taste function are either unaffected or completely lost. Facial movement

impairment is characterised by sudden paralysis and followed by a stable partial recovery. The course of vestibulocochlear nerve damage is usually progressive but cannot be predicted (Table 3.1). Therefore periodical radiological imaging is necessary for assessment of disease progression.

Treatment

A causative treatment is not available for HCI. Nevertheless, except for support and counselling, there are several important therapeutic interventions. Female patients experiencing fluctuation of their symptoms during their hormonal cycles, such as anosmia, can benefit from continuous use of oral contraceptives to avoid high blood concentration of progestagens. Moderate sensorineural hearing loss can be revalidated with hearing aids. Decompressive operations can be performed. Facial and vestibulocochlear nerve compression, in this disorder likely limited to the intrameatal part of the nerves, can be treated by decompressing the internal auditory canal via middle fossa approach¹². This intervention should be performed at young age when hyperostosis and osteosclerosis are expected to be minimal. In our patient this procedure is performed after bilateral facial palsies, however prophylactic decompression in high-risk individuals with beginning internal auditory canal encroachment can also be considered. Optic nerve decompression can be performed in case of threatened vision due to optic canal narrowing. For auditory revalidation in deaf patients an auditory brainstem implant can be considered, carefully assessing the distortion of the anatomy due to hyperostosis. Trigeminal neuropathy can be treated medically, by a percutaneous nerve block, radiofrequency ablation or by radiosurgery. There is scarce literature about the resolution of trigeminal neuralgia associated with Chiari-I malformation^{13,14} through foramen magnum decompression. If hyperostosis is the cause of downward herniation of the brain, a decompressive craniotomy might better be considered¹⁵. A decompressive craniotomy has not been performed in one of the patients but can be indicated in severe hyperostosis and maybe combined with one of the aforementioned interventions.

Conclusion

HCI should be suspected in case of adult or childhood onset of familiar facial nerve or vestibulocochlear nerve impairment. Besides audiometry, a lateral skull radiograph will often be the initial diagnostic investigation (Figure 3.5). To confirm the diagnosis a CT scan is performed (Figure 3.3). Patients generally become symptomatic in their second and third decade. Early decompressive operations of the optic, facial, and vestibulocochlear nerves are advised.

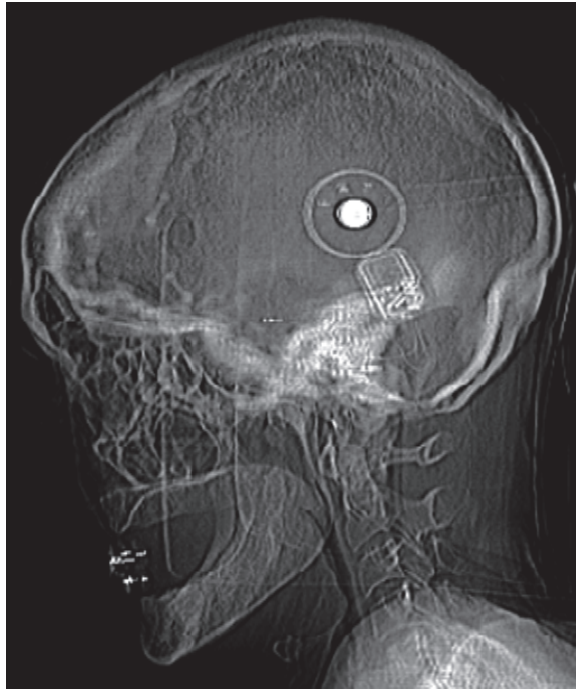


Figure 3.5 Lateral skull radiograph of individual III-7 (i.e., scout view of a CT scan). The skull base and frontal hyperostosis are the most remarkable abnormalities. The auditory brainstem implant and osteosynthesis material of the optic nerve decompression operation are visible.

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Chapter 4

Neurophysiologic, audiometric and vestibular function tests in patients with hyperostosis cranialis interna

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Abstract

Introduction

Hyperostosis Cranialis Interna (HCI) is an autosomal dominant sclerosing bone dysplasia affecting the skull base and the calvaria, characterised by cranial nerve deficits due to stenosis of neuroforamina. The aim of this study is to describe the value of several neurophysiological, audiometric and vestibular tests related to the clinical course of the disorder.

Methods

Ten affected subjects and 13 unaffected family members were recruited and tested with visual evoked potentials, masseter reflex, blink reflex, pure tone and speech audiometry, stapedial reflexes, otoacoustic emissions, brainstem evoked response audiometry and electro-nystagmography.

Results

Due to the symmetrical bilateral nature of this disease, the sensitivity of Visual Evoked Potentials (VEPs), masseter reflex and blink reflex is decreased (25-37.5%), therefore reducing the value of single registration. Increased hearing thresholds and increased BERA latency times were found in 60-70%. The inter-peak latency I-V parameter in BERA has the ability to determine nerve encroachment reliably. 50% of the patients had vestibular abnormalities. No patient had disease-related absence of otoacoustic emissions, because the cochlea is not affected.

Conclusion

In patients with HCI and similar craniofacial sclerosing bone dysplasias we advise monitoring of vestibulocochlear nerve function with tone and speech audiometry, BERA and vestibular tests. VEPs are important to monitor optic nerve function in combination with radiological and ophthalmologic examination. We do not advise the routine use of blink and masseter reflex.

Introduction

Hyperostosis cranialis interna (HCI) is a hereditary bone dysplasia (Online Mendelian Inheritance in Man 144755) first described in 1990¹ and is characterised by hyperostosis and osteosclerosis of the calvaria and skull base. This process leads to narrowing of various neuroforamina, causing cranial nerve entrapment and dysfunction of cranial nerves I, II, V, VII and VIII. Only one large Dutch family has been diagnosed with HCI to date, a pedigree is depicted in Figure 4.1. HCI has an autosomal dominant transmission pattern.

To evaluate the function of the involved cranial nerves, patients underwent a series of function tests. The goal of this paper is to correlate symptomatology to various cranial nerve function tests. In this descriptive report, we will present an overview of the results of the tests of the affected individuals (see Figure 4.2).

The test battery consisted of clinical neurophysiologic testing: visual evoked potentials (VEP); blink reflex and masseter reflex; audiometric testing: pure tone and speech audiometry, stapedial reflexes, otoacoustic emissions (OAE) and brainstem evoked response audiometry (BERA); and vestibular testing: electronystagmography (ENG).

Correspondence between objective cranial nerve tests and symptomatology or disease stage could be of prognostic value, could help for optimising treatment planning and improve counselling.

Materials and methods

Subjects

Twenty-two family members were examined, 10 of which are affected. The same patients were examined as in the earlier study about the course of the disease and the symptomatology, except the individuals indicated with # in Figure 4.1². The main reason was that the concerning children were considered to be too young. Function tests were performed in research setting. The individuals were aged 5 to 68 years at the time of examination. Written informed consent was obtained for all tested individuals.

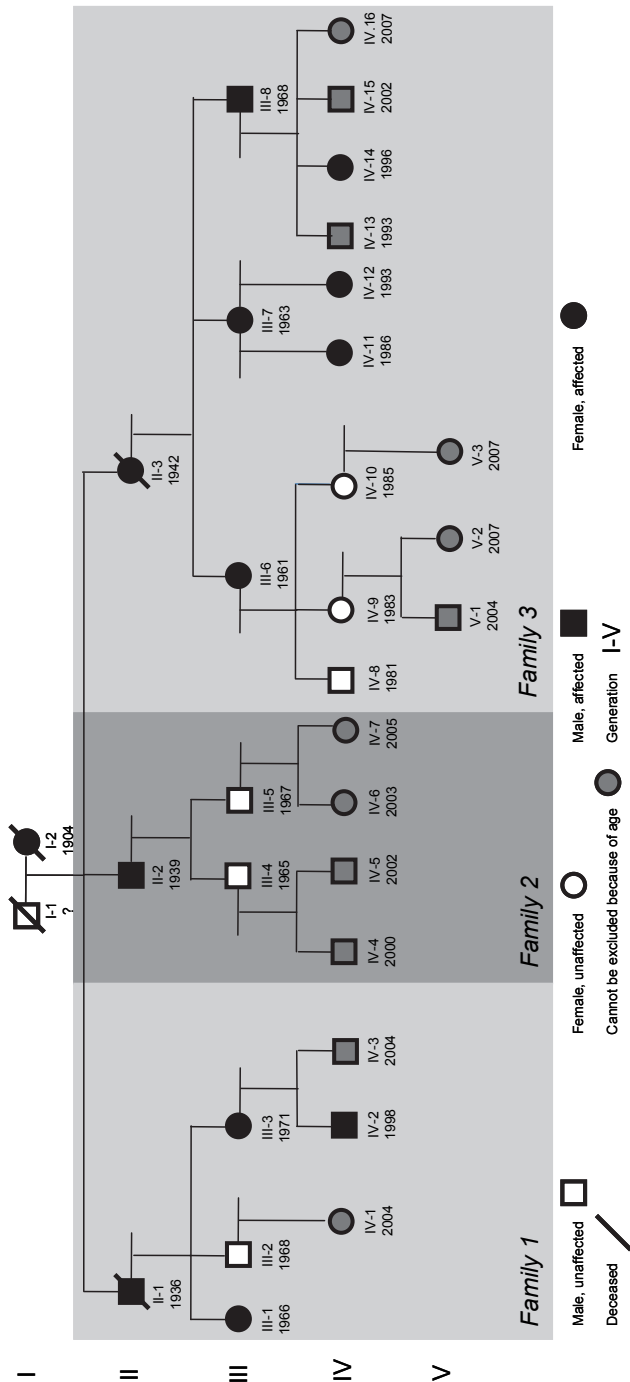


Figure 4.1 Pedigree of the affected family.

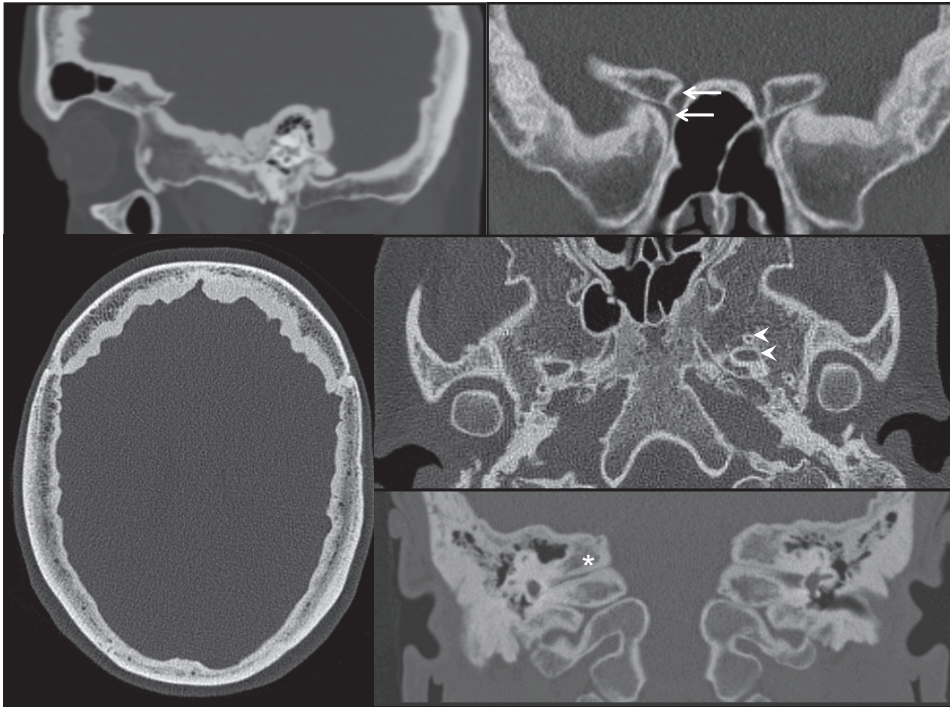


Figure 4.2 Multiple CT images of patients affected with hyperostosis cranialis interna. Upper left: sagittal image of the skull base and calvaria at the level of the inner ear. An hyperostotic endosteal layer can be seen (female mid-30s). Lower left: axial image of a markedly thickened skull. Upper right: coronal image (23-year-old female) of the greater and lesser sphenoid wings. Note narrowing of the optic canal (*upper arrow*) and the superior orbital fissure (*lower arrow*). Middle right: axial image showing the foramen rotundum (*upper arrowhead*) and the foramen ovale (*lower arrowhead*) in an 18-year-old female. Lower right: bilateral narrowing of the internal auditory canal in a 16-year-old patient (*asterisk*, coronal reconstruction).

Optic nerve

Optic nerve function was tested with pattern reversal VEP (ISCEV standard for clinical visual evoked potentials)^{3,4}, each eye stimulated individually. Seven electrodes were placed on the scalp to register potentials. Peak latencies N75, P100 and N145 were recorded. The P100 latencies were compared to laboratory reference values and classified accordingly as normal or as possible optic neuropathy and VEP outcome was correlated to clinical ophthalmologic examination.

Trigeminal and facial nerve

Trigeminal nerve function was assessed using both the masseter reflex and the blink reflex (afferent limb). To assess the masseter reflex, an active electrode was placed

bilaterally on the masseter muscle belly and a reference electrode below the mandibular angle. The reflex was elicited by a tap on the chin with a reflex hammer and recordings were made simultaneously from the right and left masseter muscles. Latencies and amplitude were recorded repeatedly and the averaged signal was measured. Prolonged latencies and left-right differences were primary outcome measures (reference value: ≤ 8.7 ms).

The efferent limb of the blink reflex was used as a parameter to assess facial nerve function and was evoked by electrical stimulation of the supraorbital nerve transcutaneously over the supraorbital foramen. Responses from both orbicularis oculi muscles were recorded with two pairs of electrodes (bilaterally, placed two cm under the eyes) and a ground electrode under the chin. The registration consisted of latencies from an early ipsilateral response to the stimulated nerve (R1-peak) and a late bilateral response (R2-peak). Waveforms were analysed and left-right differences were compared with laboratory reference values (reference values $R1 \leq 13.0$ ms, $R2_{\text{ipsi}} \leq 40.0$ ms, $R2_{\text{contra}} \leq 41.0$ ms). The House-Brackmann (HB) score⁵ was assessed by two trained clinicians in all cases. The outcome was correlated to the HB score and the presence of stapedial reflexes.

Vestibulocochlear nerve

Pure tone and speech audiometry

Patients underwent pure tone air and bone conduction audiometry to determine hearing threshold levels. Frequencies ranged from 250 Hz to 8.0 kHz. Intensities were measured in dB HL (ISO 1975). Pure Tone Average (PTA) was determined as the average threshold at 1.0, 2.0 and 4.0 kHz. For speech audiometry we used validated Dutch lists of monosyllabic words (consonant-vowel-consonant words, Dutch Association of Audiology). The subject listened to one list of words at a set sound level. The percentage of phonemes repeated correctly was scored and followed by a different list at 10 to 20 dB intervals until maximum phoneme recognition percentage was achieved. The Speech Reception Threshold (SRT) was defined as the sound intensity required for the subject to repeat 50% of the presented phonemes correctly.

Tympanography, stapedial reflexes and otoacoustic emissions

Tympanometry was performed using a 226 Hz probe tone at 65 dB SPL. The results are not related to HCI, but can influence OAE and stapedial reflex results. Reflexes were elicited at 0.5, 1.0, 2.0 and 4.0 kHz, with stimulation levels between 70 and 110 dB HL (hearing level). Click-evoked otoacoustic emissions (CEOAEs) were recorded. We presented clicks at 80–85 dB SPL, tested frequencies were 1.0, 1.4, 2.0, 2.8 and 4.0 kHz. CEOAEs were considered normal if deemed present on at least two frequency bands.

Brainstem evoked response audiometry

Rarefaction polarity, and in two patients alternating polarity, click stimuli of 100 ms were presented monaurally through headphones at sound intensity levels varying from 70 to 85 dB nHL at a rate of 11.7 to 15.7/s. Subjects underwent three to five runs of 1,000 to 1,500 clicks per ear. Filter settings were 30 Hz–3.0 kHz. The analysis time window was 20 ms. One electrode was placed on the vertex and electrodes were placed on the mastoid process bilaterally to register responses. Responses were averaged for each run and inter-peak latencies were calculated and compared to normative values⁶. The main interest was in the latency interval between peaks I and V⁷.

Vestibular function tests

Smooth pursuit, optokinetic nystagmus, saccades, torsion swing, velocity step and caloric testing were performed. Eight electrodes were placed on all four sides of both eyes to detect the corneoretinal potential when smooth pursuit, optokinetic nystagmus, saccades, torsion swing, velocity step and caloric testing were performed. The reference electrode was placed on the forehead.

Smooth pursuit was tested with a sinusoidally moving target ($f=0.2$ Hz, peak amplitude 10°) Primary measures were position gain and phase.

Spontaneous, fixation and gaze evoked eye movements were quantified. Optokinetic nystagmus was tested with a horizontally moving random dot pattern on the wall. Velocities applied were $5^\circ/\text{s}$ up to $35^\circ/\text{s}$ with intervals of $5^\circ/\text{s}$. Each velocity, both leftwards and rightwards, was presented for 1 minute. To evaluate the vestibulo-ocular reflex in complete darkness with eyes open, rotational testing was performed. The torsion swing rotation test (with and without fixation to score the fixation suppression index) was applied using a stimulus frequency of 0.1 Hz with a peak velocity of $60^\circ/\text{s}$. The second rotational test stimulus was using a velocity step test profile, both clockwise and anti-clockwise. A subthreshold acceleration of $1.5^\circ/\text{s}^2$ was applied until a peak velocity of $100^\circ/\text{s}$ was achieved. This velocity was sustained until 10 seconds after the perrotatory nystagmus had disappeared completely and then a deceleration impulse of $100^\circ/\text{s}^2$ was applied until standstill. The post-rotatory gain, time constant and response symmetry (contrast function comparing clock-wise and anti-clockwise responses) were calculated.

Caloric testing was performed to evaluate horizontal semicircular canal function. The patient was in supine position, with the head tilted 30° in flexion. Each ear was irrigated with water for 30 seconds (30°C and 44°C) with a total volume of 250 ml. Nystagmus preponderance and side difference were calculated according to the Jongkees formula⁸. Excitability was considered reduced when the sum of responses to the cold and warm irrigation on one side was below $15^\circ/\text{s}$. A nystagmus preponderance of more than 25% and a side difference of more than 20% were considered pathological.

Box 1. The course of disease of patient III-3 (♀, 1971) is exemplary for HCI. At the age of 15 she developed a right-sided facial nerve paralysis, recovering to House-Brackmann grade III in six months and still present today. She has subjective hearing loss and tinnitus since age 18. She reported total anosmia during both pregnancies and currently her sense of smell and taste are bilaterally absent. Left trigeminal nerve function is lost without signs of trigeminal neuralgia. Visual symptoms were never reported.

Radiological skull abnormalities had been observed since age 14. A thick inner table and a narrowed internal acoustic canal, foramen ovale and superior orbital fissure were seen bilaterally. Testing revealed mild hearing loss with a pure tone average of 25 (right side) and 15 dB HL (left side), with an increased speech reception threshold at the right side and an abnormal BERA. CEOAEs were present bilaterally indicating normal cochlear function. Vestibular testing revealed right labyrinth hyporeflexia. The absent blink and stapedial reflexes on the right side indicate facial nerve dysfunction. Fundoscopy and ultrasonography revealed right-sided asymptomatic papilloedema. Masseter reflex was normal.

The general order of pathological onset, either by symptoms or testing, is summarised as follows: skull thickening, *subclinical* vestibulocochlear nerve dysfunction, facial nerve palsy, *clinical* vestibulocochlear nerve dysfunction and – in a random order – ophthalmic nerve, trigeminal nerve and optic nerve dysfunction.

Results

Optic nerve

Eight out of ten patients were tested using pattern reversal VEPs (Figure 4.3). Two patients did not take part. Moreover, due to HCI related blindness, it was not possible to obtain a right-sided VEP from patient III-7 (♀, 1963); patient IV-1 (♀, 2004) underwent a flash VEP test because of her young age (normal response). None of the examined patients had a visual acuity lower than 20/25 cum correctione.

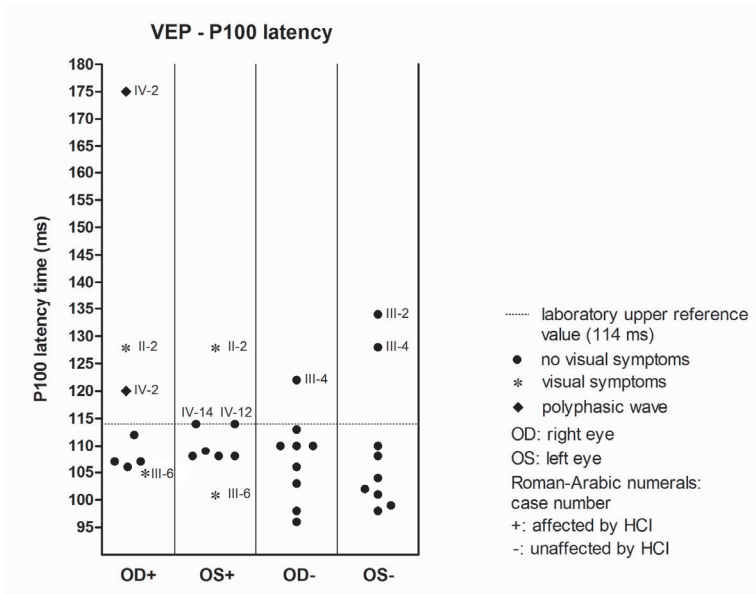


Figure 4.3 Scatter plot of VEP results in patients and the unaffected family members.

Two of the unaffected family members had unexplained increased latency times, one of his left optic nerve (III-2, ♂, 1968) and one bilaterally (III-4, ♂, 1965).

Patient IV-2 (♂, 1998) showed a pathological double VEP P100 waveform from his right eye (visual acuity of 20/25, refractory origin, no other symptoms). The optic canals were not extremely narrowed on CT scan, leaving no explanation that could link the VEP results to HCI-related compression neuropathy. Patient II-2 (♂, 1939) had bilaterally prolonged VEP latency times and diffuse loss of peripheral vision. The CT scan showed mild encroachment of the right optic canal but no abnormalities of the left optic canal. On the other hand, one patient with a nearly obliterated left optic canal (diameter 0.7 mm) on the CT scan (III-7, ♀, 1963) had no visual symptoms and a normal P100 latency.

Trigeminal and facial nerve

All masseter and blink reflexes were normal in the unaffected group. Eight out of ten patients underwent masseter and blink reflex testing (Figure 4.4). Three individuals, all female, reported trigeminal nerve related complaints. One patient had an abnormal masseter reflex latency time unilaterally. Patient III-7 (♀, 1963) had trigeminal nerve symptomatology and a unilateral prolonged latency. Patient IV-11 (♀, 1986) had bilaterally prolonged masseter reflex latencies and she reported new-onset bilateral trigeminal nerve symptoms in the follow-up period. Concerning the masseter reflex, a

trend was observed of latencies near the upper level of normality in the affected group as opposed to the unaffected subjects.

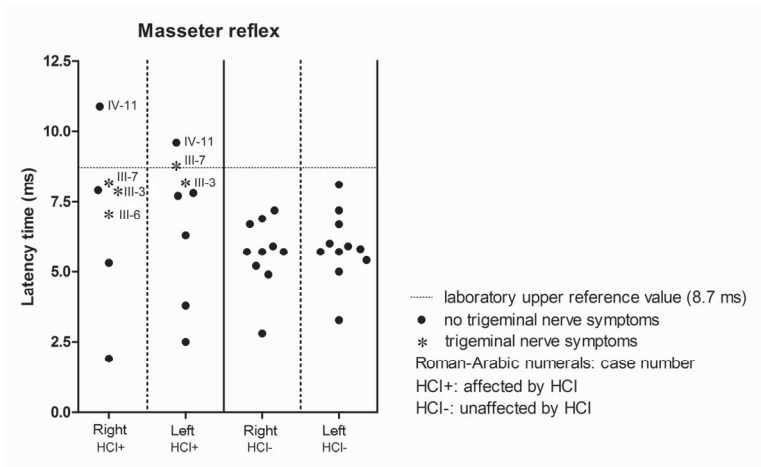


Figure 4.4 Scatter plot of masseter reflex results in patients and the unaffected family members.

The blink reflex revealed abnormalities in three patients (symptomatic individuals III-7 and III-3 and asymptomatic patient IV-2). In these individuals the tests results could be deducted to facial nerve dysfunction (efferent limb) rather than trigeminal nerve dysfunction. At the time of the investigations there were 5 patients with unilateral and 1 with bilateral clinical facial nerve dysfunction (Table 4.1).

Individual III-7 did not show R1 responses (bilaterally) on blink reflex registration, indicating a laesion of both facial nerves. According to Aramideh *et al.*, absent R1 and present R2 responses can occur in brainstem laesions and partially recovered facial neuropathies. The combination of nearly obliterated internal acoustic canals on CT scan and a history of facial palsy makes the latter most likely⁹. Stapedial reflexes could not be elicited due to deafness. Blink reflexes were also abnormal for patients III-3 (♀, 1971, polyphasic R1 response on the right) and IV-2, (♂, 1998, left-sided latencies elongated compared to the right side). Patient IV-14 (♀, 1996) underwent bilateral internal auditory canal decompression to prevent deterioration of facial nerve function. Post-operatively she has an HB score of 1 (right) and 2 (left), normal blink reflex and stapedial reflex activity. No pre-operative blink reflex or stapedial reflex test results were available for her.

Table 4.1 Clinical data on facial and vestibulocochlear nerves.

Case	Sex	Age during testing	House-Brackmann (R / L)	Subjective hearing loss (R / L)	Tinnitus (R / L)	Loss of balance and/or unsteady gait	Remarks
IV-2	M	9	1 / 1	- / -	- / -	-	
IV-14	F	11	1 + / 2	- / -	+ / +	-	Internal auditory canal decompression L+R
IV-12	F	14	1 / 1	- / -	- / -	-	
IV-11	F	21	1 / 1	- / -	- / -	-	
III-3	F	36	3 / 1	+ / -	+ / -	-	Ageusia
III-8	M	39	1 + / 2	- / +	- / +	-	Dysgeusia left
III-1	F	41	1 / 1 +	+ / +	- / -	+	Bilateral dysgeusia
III-7	F	44	4 / 4	+ / +	- / -	+	Facial synkinesis, ageusia, deaf due to HCI, auditory brainstem implant
III-6	F	45	1 + / 2	+ / +	+ / +	+	Epiphora, ageusia
II-2	M	68	2 / 1	+ / +	+ / -	-	Epiphora, radical mastoidectomy AS

† Recovered completely after prior facial nerve palsy.

Vestibulocochlear nerve

Pure-tone audiometry and speech audiometry

Six out of 10 patients were diagnosed with disease-related neural hearing loss (described in Table 4.1). No specific frequency range was most commonly affected. Speech intelligibility is congruent to PTA results, no roll-over has been observed.

Tympanography and OAEs

Three patients had a hypermobile tympanic membrane (maximal compliance of the tympanic membrane >1.6 cc at tympanic peak pressure), one patient showed a bilaterally flat tympanogram (II-2, ♂, 1939, modified radical mastoidectomy) and one had a negative middle ear pressure. OAEs were assessed in nine people. Absent OAEs could in no case be deducted to an abnormal tympanogram. Emissions were completely absent in one out of nine subjects (age-related hearing loss).

Stapedial reflexes

Nine patients were tested, four did not have stapedial reflexes: patient II-2 (♂, 1939) because of a bilaterally flat tympanogram (and radical mastoidectomy), patient III-7 (♀, 1963) due to bilateral deafness, IV-2 (♂, 1998, left-sided absence) with an ipsilateral hypermobile tympanic membrane (possibly explaining the absence of stapedial reflexes) and patient III-3 (♀, 1971) with absent reflexes at the right side (facial palsy) and the left side (hypermobile tympanogram). Only the latter patient had an absent

stapedial reflex that could not be explained by deafness or abnormalities found using tympanography, indicating dysfunction of the ipsilateral facial nerve and/or bilateral vestibulocochlear nerves for the tested frequencies.

BERA

Eight patients underwent BERA examination. We defined prolonged latency times as being more than two standard deviations from normal values according to Stockard *et al.*⁶. Inter-peak latencies I-V were prolonged bilaterally in four patients and unilaterally in one patient (Figure 4.5). BERA abnormalities occurred earlier than PTA abnormalities in all patients, except for patient III-6 (♀, 1961).

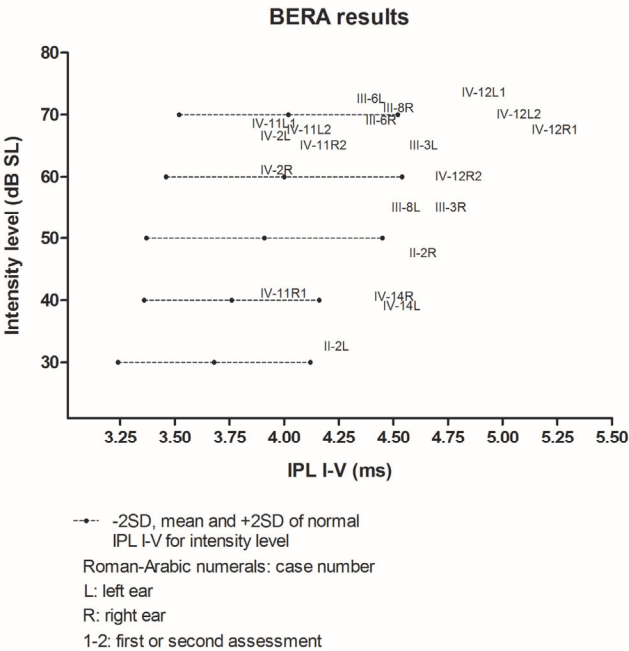


Figure 4.5 BERA results in tested patients.

Vestibulogy

Vestibular testing in all seven tested patients revealed no central pathology. We did not find a spontaneous or gaze evoked nystagmus. The optokinetic nystagmus, smooth pursuit and saccade testing were normal for all. One-sided hypofunction of the labyrinth was found in one patient, three patients had a bilateral hypofunction and two had normal test results (Figure 4.6). Abnormal test results consisted of subnormal

calorisation, yet with normal rotational tests. Test quality in one subject was dissatisfactory and as such mild lateral canal hyporeflexia could not be excluded. Bilateral absence of vestibular function was clinically diagnosed in patient III-7 (♀, 1963, positive head impulse tests, deaf).

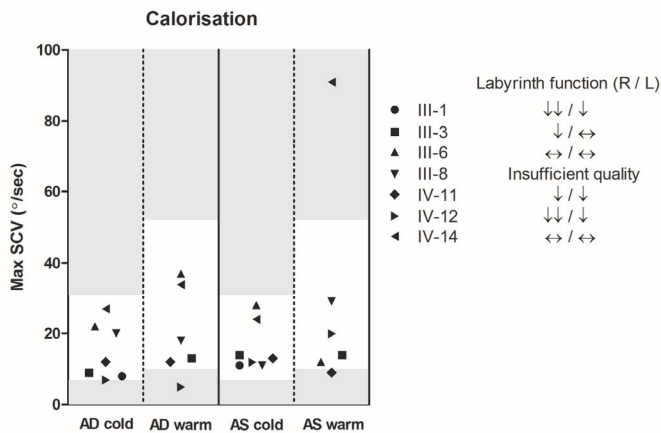


Figure 4.6 Calorisation in affected patients.

Discussion

Optic nerve

The use of VEPs does not seem to be clear-cut, since some patients without radiological abnormalities have VEP abnormalities and vice versa. Prolonged VEP latencies with significant radiographic optic canal involvement justifies strict follow-up. On the other hand, prolonged VEP latencies without significant optic canal encroachment have been observed as well. This could be a predictor for future symptoms or a false positive finding.

Earlier literature concerning compressive opticopathy report VEPs as a highly sensitive screening tool for optic pathway gliomas¹⁰, detecting pathology prior to radiological modalities, however leading to many false positives¹¹. Haines *et al.* and Thompson *et al.* demonstrated that VEP abnormalities often precede clinical symptoms or neuro-imaging signs in osteopetrosis^{12,13}. On the other hand, Tsaloumas *et al.* found a low VEP sensitivity in patients with dysthyroid optic neuropathy with only 23% of affected eyes having a delayed P100 component¹⁴.

It seems that a single P100 latency registration without radiographic signs of nerve compression cannot be used as a general predictor of nerve function in different compressive optic nerve disorders. A longitudinal follow-up with VEP examination, combined with symptomatology and regular imaging, would be valuable to monitor progressive compression of the nerve due to occlusion of the optic canals. We advise VEP testing whenever a patient reports (increased) visual complaints or the CT scan shows significant decrease in optic canal diameter. We advise surgical intervention (optic nerve decompression) in two circumstances. In the first place in case of (sub)acute vision loss with proven radiographic optic canal encroachment. Furthermore we advise decompression even when vision seems to be stable, however when there is significant deterioration of the VEP results, again with radiographic proof of optic canal narrowing. To perform decompression in case of radiologic narrowing of the canal alone, is not advised. This is in line with the consensus about the management of optic canal involvement in patients with fibrous dysplasia or McCune Albright syndrome¹⁵.

Trigeminal nerve

Although trigeminal nerve symptomatology is not very common in HCI patients, the masseter and blink reflexes offer relatively easy screening of the involvement of this cranial nerve. Since all patients with trigeminal nerve symptoms experienced impairment of at least the mandibular nerve (NV₃), a combination of the masseter and blink reflex should readily demonstrate trigeminal abnormalities in our patient group^{9,16}.

Several compressive trigeminal neuropathies are known, most notably neurovascular conflicts (often by the superior cerebellar artery)^{17,18} and cerebellopontine angle tumors¹⁶. No literature was found on the systematic use of masseter reflex testing in patients with trigeminal nerve compression. Slightly more is known about the blink reflex. Kimura reported abnormalities in 59% of the responses with a compressive lesion of the trigeminal nerve¹⁹. Eisen and Danon described blink reflex abnormalities in ten patients with cerebellopontine angle tumours (≥ 20 mm) and trigeminal nerve symptoms. Blink reflex results confirmed trigeminal dysfunction in 80% of these patients (8/10)²⁰.

Most compressive processes are unilateral and left-right latency differences are observed. Since HCI is a bilateral symmetrical process, equally prolonged latency times are measured bilaterally, decreasing sensitivity of both masseter and blink reflex. In the case of the masseter reflex, we did notice a trend that most of our patients, especially when symptomatic, had latencies near the upper reference value. A single neurophysiologic evaluation of the trigeminal nerve seems to add little value to clinical assessment and imaging. Serial measurements (combined with clinical and imaging) could be useful to detect progressive dysfunction of the trigeminal nerve.

Facial and vestibulocochlear nerve

There is a significant decrease in size of both the porus and fundus of the internal acoustic canal of HCI affected patients²¹. Due to the slow progression of the condition, few patients describe a loss of hearing or vertiginous signs, the latter mostly because of central compensation of the decreased labyrinth function. Facial nerve palsy is the first clinical symptom reported by most HCI patients, occurring between 8 and 33 years². Based on the fact that encroachment of the facial nerve is located primarily in the internal acoustic canal²², all nerve functions are expected to be affected equally.

Facial and subjective vestibulocochlear nerve complaints are very common in our patients as the age increases (Table 4.1). The sidedness of facial nerve dysfunction is in agreement with vestibulocochlear symptoms. The facial nerve palsy is an acute symptom and therefore noticed much easier than the slowly decreasing function of hearing and the vestibular apparatus. In the literature, the stapedial reflex has been reported to be preserved during an episode of facial palsy. The lower susceptibility of the stapedial nerve is probably due to the smaller diameter of stapedial nerve fibers than those in the facial nerve trunk²³. In general, the order of dysfunction due to internal auditory canal narrowing would be: subclinical vestibulocochlear dysfunction, followed by acute facial palsy and later clinical vestibulocochlear dysfunction. This pattern is reflected by our results.

No patients with recovered facial nerve function after prior facial palsy had prolonged blink reflexes. Out of the 5 patients with (4 unilateral, 1 bilateral) facial nerve symptoms at the time of investigation, 3 reflexes indicated facial neuropathy (sensitivity 3/6: 50%). These results are similar to blink reflex outcome for different indications, for example vestibular schwannomas. These studies show that the difference in R1 latency between left and right was the most useful parameter to illustrate the effect of chronic compression, concluding to a sensitivity of 56%. However, as opposed to (most) schwannomas, HCI is a more or less bilaterally symmetrical process and will therefore yield equally prolonged latency times. According to Normand *et al.* - left-right differences are not taken into account - this would decrease the sensitivity to less than 40%²⁴.

BERA results are a relatively adequate reflection of the internal auditory canal diameter (Figure 4.7). As the internal auditory canal diameter is decreased to less than 2 mm, latency times increase pathologically. Even with functional hearing, abnormal BERA results are registered when the canal size is severely decreased. Therefore BERA is useful to monitor cochlear nerve function and it is an essential diagnostic test in this disease.

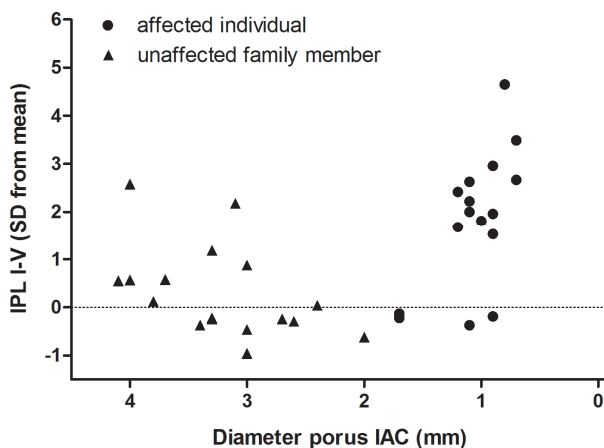


Figure 4.7 BERA IPL I-V times versus internal auditory canal (IAC) diameter.

The use of BERA is widespread and its value is undisputed, however with the increasing availability of MRI the use of BERA declines. In the literature, its sensitivity for diagnosing vestibular schwannomas ranges from 58% to 100%, depending on the amount of compression on the vestibulocochlear nerve²⁵⁻²⁷.

Central vestibular pathology is not expected in HCl. Repeated calorisation is a useful method to monitor vestibular nerve function until complete vestibular areflexia. In case of vestibular areflexia residual function might be found upon rotational tests. Vestibular testing using calorisation has revealed sensitivity of 77-86% for vestibular schwannomas %^{25,28,29}, although Marangos *et al.* found a sensitivity of 40% for cerebellopontine angle tumours in general²⁷ (see Table 4.2).

As OAEs are a measure of outer hair cell function and not cochlear nerve function, emissions are present in patients even with neural disease-related hearing loss³⁰⁻³³.

Table 4.2 Test data on facial and vestibulocochlear nerves.

Case	Blink reflex*	Stapedial reflex*	PTA bone threshold [§] (dB)		Speech intelligibility		OAEs* (R/L)	BERA (IPL I-V) (R/L)	Labyrinth function (R/L)
	(R/L)	(R/L)	AD	AS	AD	AS			
II-2	+ / +	N/A	0-45		5-50		Congruent to PTA	- / -	↑ / ↑
IV-2	+ / -	+ / †	Normal		Normal		+ / +	↔ / ↔	N/A
IV-14	+ / +	+ / +	Normal		Normal		+ / +	↑ / ↑	↔ / ↔
IV-12	+ / +	+ / +	5-15	0-20	Congruent to PTA		+ / +	↑ / ↑	↓ ↓ / ↓ ↓
IV-11	+ / +	+ / +	Normal		Normal		+ / +	↔ / ↔	↓ / ↓
III-3	- / +	- / †	5-25	Normal	Normal		+ / +	↑ / ↑	↓ / ↔
III-8	N/A	N/A	Normal		Normal		‡ / ‡	↔ / ↑	Insufficient test quality
III-1	N/A	N/A	10-35	25-40	N/A		N/A	N/A	↓ / ↓
III-7	- / -	- / -	Deaf		Deaf		N/A	No response	N/A
III-6	+ / +	+ / +	10-30	5-40	Congruent to PTA		+ / ‡	↔ / ↔	↔ / ↔

* + normal registration, - absent or abnormal registration; § bone conduction threshold was used, because there were individuals with non-disease related conductive hearing loss; PTA pure tone average; † absent reflex, possibly due to tympanographic abnormality; ‡ OAE response in one frequency band only; ↔ normal IPL or calorisation; ↑ or ↓ increased or decreased latency or calorisation; N/A not assessed.

Conclusion

In summary, selected function tests in HCI are useful. We advise yearly monitoring of vestibulocochlear nerve function with tone and speech audiometry, BERA and vestibular function tests in young patients. In case of acute deterioration of tone and/or speech audiometry or in case of acute facial nerve palsy in combination with radiographically proven internal auditory canal narrowing decompression is advised. We advise to perform internal auditory canal decompression – even without (further) hearing loss – in case of deterioration of BERA and/or deterioration of the vestibular function test results in combination with radiographic proof of internal auditory canal encroachment. Facial nerve palsy at young age due to internal auditory canal encroachment is so common in HCI that decompression can even be considered preventively, when internal auditory canal narrowing is first observed in young individuals³⁴. Analogous to the facial and vestibulocochlear nerve management, optic nerve decompression is advised in case of acute vision loss with proven optic canal narrowing in a (sub)acute setting or in case of deterioration of serial VEP results in combination with proven radiographic narrowing of the optic canal. Yearly performed visual evoked potentials are advised to monitor the optic nerve function, in case of marked narrowing of the optic canal/superior orbital fissure (CT) or in case disease-specific abnormalities upon ophthalmologic examination. We do not advise the routine use of blink and masseter reflex.

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Chapter 5

Imaging features and progression of hyperostosis cranialis interna

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Abstract

Introduction

Hyperostosis cranialis interna (HCI) is an autosomal dominant sclerosing bone dysplasia affecting the skull base and the calvaria, characterised by cranial nerve deficits due to stenosis of neuroforamina, whereby the mandible is affected to a lesser extent. The aim of this study is to describe the specific radiologic characteristics and course of the disorder.

Methods

Computed tomography scans of affected individuals within 1 family were analysed and compared with scans of their unaffected family members and with an age- and gender-matched control group. Linear measurements were performed of the inner table (tabula interna), the medulla (diploë) and the outer table (tabula externa) of different skull locations, and attenuation (density) measurements of the same regions were recorded. Neuroforamina widths were recorded as well.

Results

There is significant thickening of the skull in the frontal, parietal, temporal and occipital regions, which is mainly due to thickening of the inner table of the skull. The density of the deposited hyperostotic bone is lower than normal cortical bone.

Conclusion

HCI is a bone dysplasia with abnormalities confined to the craniofacial area. The hyperostotic bone is less dense than normal cortical bone. The observed radiological abnormalities explain the possible impairment of the olfactory, optic, trigeminal, facial and vestibulocochlear nerves.

Introduction

Hyperostosis cranialis interna (HCI) is a hereditary bone disorder characterised by progressive skull base osteosclerosis and endosteal hyperostosis of the calvaria (Figure 5.1). Clinical features and the course of the disorder are described in one kindred (Figure 5.2) in the Netherlands^{1,2}. Patients generally become symptomatic in their late first, second or third decade due to cranial nerve entrapment. Facial palsy, sensorineural hearing loss, vestibular symptoms, olfactory impairment, optic impairment and trigeminal neuralgia are the observed symptoms.

Although the emphasis in research of bone dysplasias dysplasias is shifting towards detection of the genetic and molecular underlying defects³, knowledge of the radiologic features is crucial to diagnose the disorder and to assess progression. The international classification of bone dysplasias is still based on radiologic hallmarks⁴.

The aim of this study is to describe the initiation of the abnormalities in young patients, to describe the evolution of these abnormalities throughout life and to quantify differences between HCI patients and control subjects to facilitate early diagnosis. Moreover better counselling can be provided if the course of the disorder can be more precisely predicted.

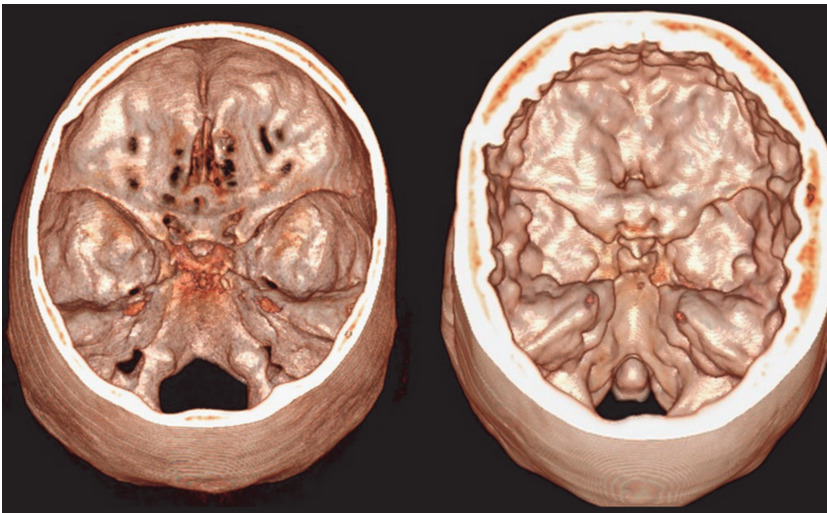


Figure 5.1 3D-reconstruction of a normal skull base and one of a patient with hyperostosis cranialis interna. The left image is an unaffected individual in which all neuroforamina can be identified. The right image is an affected individual with thickened calvaria and a bulgy skull base; neuroforamina are hardly visible.

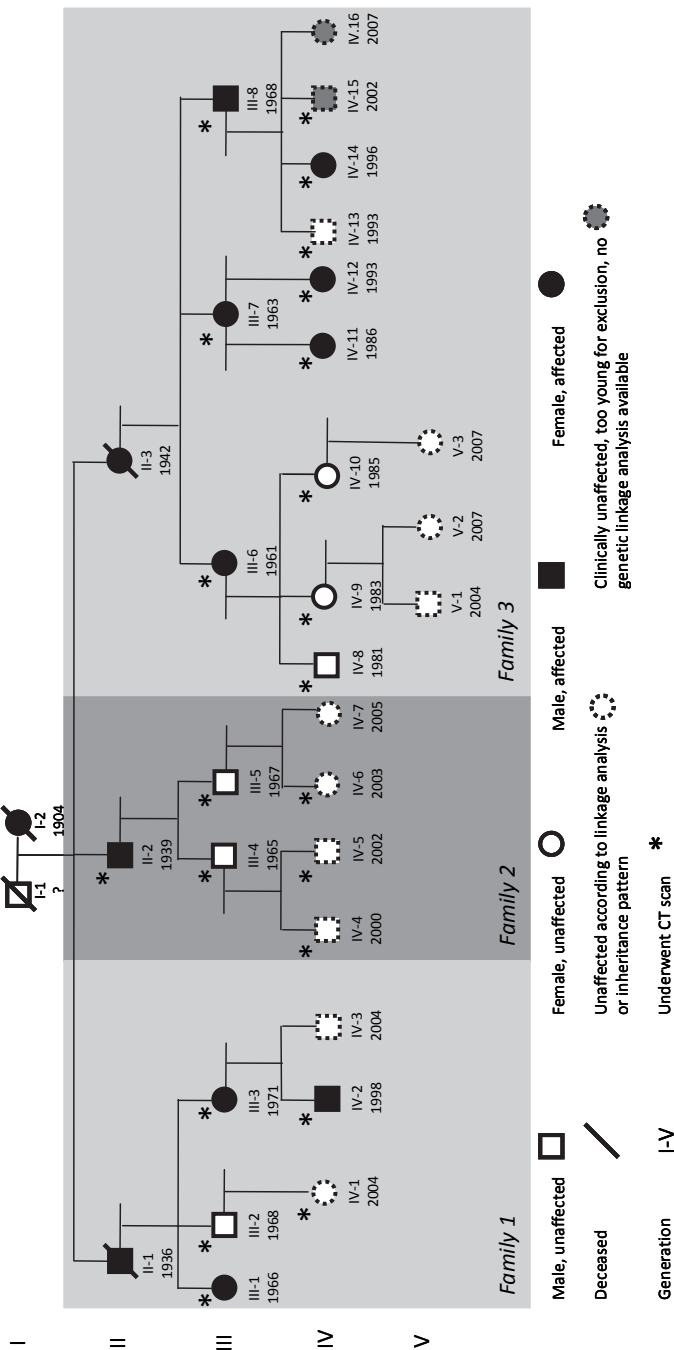


Figure 5.2 Pedigree of the affected kindred. An asterisk is placed if the individual has undergone a CT scan.

Methods

Subjects

Twenty-two family members – affected group 1 and unaffected group 2 – underwent a high-resolution CT. Twenty-one control subjects were selected retrospectively, matching for gender and age: group 3 matching group 1 and group 4 matching group 2. These CT scans were selected from the hospital database, scans performed with appropriate settings (≤ 1 mm slice thickness) and without bone abnormalities were considered suitable. The local medical ethics committee approved the protocol (09-4-050.4/pl). All HCI family members gave written informed consent.

CT imaging and analysis

CT scans were performed using helical scanners with ≤ 1 mm slice thickness in the axial plane. The local Picture Archiving and Communications System (PACS) was used for analysis. A protocol for standard measuring was used as follows. Thickness of the frontal, parietal and occipital regions of the skull were measured in the median line and 10 and 20 mm to the right. This was done at various heights resulting in 10-15 measurements per region under magnification to avoid measuring errors. Thickness of the inner table and outer table of the skull were measured at the same locations. In addition, skull thicknesses were measured at the coronal and lambdoid sutures in the axial plane. Thickness of the inner table of the frontal skull base was measured (sagittal plane, level of the orbital apex), as well as the middle fossa inner table (coronal plane, level of optic chiasm), clivus, and dorsal foramen magnum (sagittal plane, midline).

The diameter of a selection of cranial nerve foramina were measured: the porus and fundus of the internal auditory canal, the optic canal (coronal plane) and the Vidian nerve canal (axial plane) (Figure 5.3).

Bone density was determined in Hounsfield units (HU) in different regions of interest (ROI). Screening measurements were performed in ROIs in all bone layers: frontal and occipital bone (axial plane, halfway between skull base and vertex, left, right and median), parietal bone (coronal plane, bilaterally, superior to the mastoid, and halfway skull base to vertex), greater wing of the sphenoid and apex of the petrosal bone (axial plane, bilaterally). To rule out the influence of regional heterogeneous bone density, specific regions were measured (if identifiable) with freehand ROIs (Figure 5.3C): inner table, outer table and diploë of both the frontal and parietal bones, diploë and inner table of the greater sphenoid wing, (medulla of) clivus, (medulla of) lateral orbit, and sphenotemporal and tympanosquamosal suture and, if present, exostoses of the mandible.

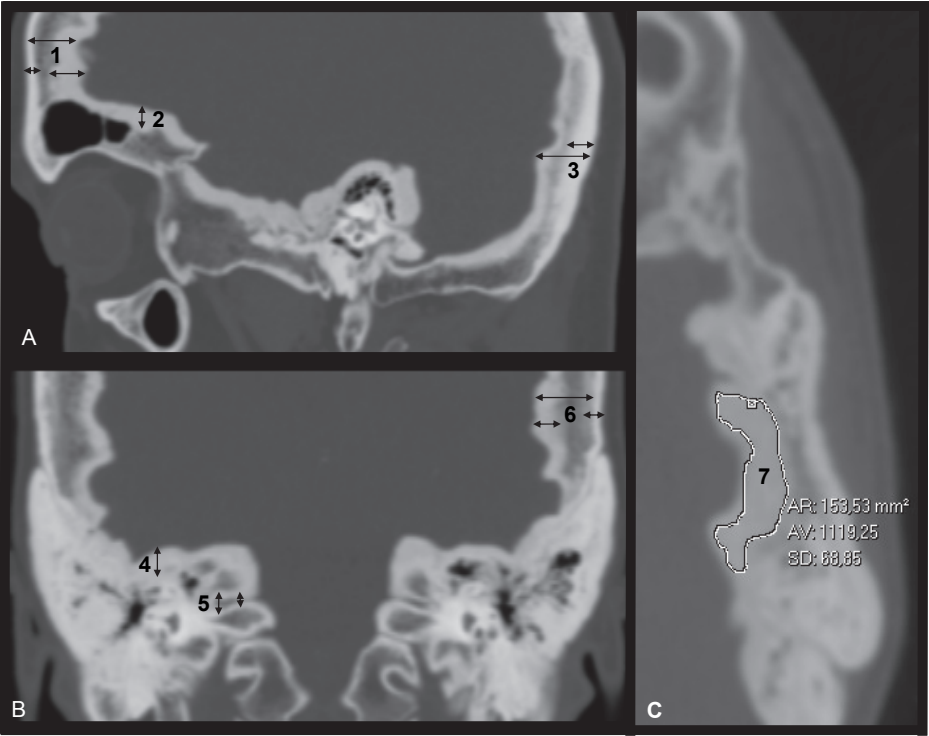


Figure 5.3 Simplified examples of different measurements. A and B: linear measurements of skull thickness and neuroforamen width. C: density measurement of freehand ROI at the inner table of parietal bone. 1: frontal bone measurements, 2: frontal skull base inner table thickness, 3: occipital bone measurements, 4: middle skull base inner table thickness, 5: internal auditory canal measurements, fundus = lateral part, porus = medial part, 6: parietal bone measurements and 7: parietal inner table density measurement.

Statistical analysis

The study group was divided into group 1 and 2, based on diagnosis. Group means of metric measurements (thicknesses and widths) and density measurements were calculated. The Kolmogorov-Smirnov test was applied to test whether variables with continuous metric values had a normal distribution. Groups 1 and 3, and groups 2 and 4, were compared applying Kruskal-Wallis and Mann-Whitney rank tests when the data could not be considered as normally distributed, otherwise with paired *t* tests. To account for physiologic differences in the size of male and female skulls, the same analyses were performed with the ratio *inner table* : *total thickness* for the same locations. In addition, the same analyses were repeated after censoring the individuals under age 18 to rule out the effect of obvious skull (base) thickening not yet being present in young affected individuals.

The influence of age was assessed with the Pearson correlation or Spearman rank coefficient correlation test, depending on whether normality could be assumed. Analysis of covariance was performed (univariate ANCOVA) to assess the influence of gender. Due to the small group sizes, adjustment for gender and age did not occur simultaneously.

Bone density was analysed in the same manner as the linear measurements. Group 1 and 3 were compared using paired *t* tests. The inner table of the greater sphenoid wing and the 3 components of the parietal bone could not be separately measured, in most cases, in group 3 and therefore we chose to consider the frontal bone (inner table) values of group 3 as reference values.

All data were analysed with SPSS version 16 (SPSS, Chicago, Illinois).

Results

Ten family members displayed abnormalities on their CT scan (group 1, mean age 32.8, range 9-68), whereas 12 family members did not (group 2, range 3 to 42). Of these 12 family members in group 2, 6 were children under the age of 18 years, which is the age an individual is considered to be unaffected, in cases in which radiological abnormalities are absent (Table 5.1). Based on genetic linkage analysis, 5 can be considered unaffected. No genetic analysis was available for individual IV.15; hence, this individual was excluded. The mean age of group 2 was 20.3. The control group that matches the affected family members is group 3 (mean age 30.8, range 7 to 67). The group that match the unaffected family members is group 4 (mean age 17.0, range 3 to 45).

Linear measurements

Mean measurements of each location are listed by group in Table 5.2. Mean values were found to be significantly higher in HCI patients compared with their control group for the following outcome parameters: frontal total, frontal inner table, frontal outer table, parietal total, parietal outer table, occipital total, occipital inner table, frontal skull base, middle skull base, foramen magnum, coronoid suture and lambdoid suture. Significantly lower mean values were found in the porus of IAC and the fundus of IAC. For 7 outcome parameters group 2 had significantly higher mean values than group 4: frontal inner table, frontal outer table, occipital inner table, frontal skull base, middle skull base, foramen magnum, and clivus.

Table 5.1 Baseline characteristics.

Group 1 Fam + HCl +				Group 3 Matches group 1			Group 2 Fam + HCl -				Group 4 Matches group 2		
Sex	Age	Pedigree		Sex	Age		Sex	Age	Pedigree		Sex	Age	
1	M	9	IV.2	1	F	7	1	F	3	IV.1	1	F	3
2	F	10	IV.14	2	M	9	2	M	4	IV.15	2	M	5
3	F	13	IV.12	3	F	11	3	F	4	IV.6	3	M	5
4	F	22	IV.11	4	F	20	4	M	5	IV.5	4	F	6
5	F	36	III.3	5	M	31	5	M	7	IV.4	5	M	9
6	M	39	III.8	6	M	39	6	M	14	IV.13	6	M	12
7	F	42	III.2	7	F	39	7	F	22	IV.10	7	F	20
8	F	44	III.7	8	F	42	8	F	23	IV.9	8	F	24
9	F	45	III.6	9	F	43	9	M	25	IV.8	9	M	28
10	M	68	II.2	10	M	67	10	M	38	III.2	10	M	30
							11	M	40	III.5	11	M	45
							12	M	42	III-4			
Mean age		33		Mean age		31	Mean age		20		Mean age		17
							(without IV.15)						

M=male; F=female; Age=age of scan; [] excluded, diagnosis uncertain; unaffected according to genetic linkage analysis; Fam = family member

All total skull thickness measurements (frontal, parietal and occipital mean values) were found to be higher for males in group 2, 3 and 4. In group 1, the female group had higher mean values, however these differences were not statistically significant. *Inner table* : total thickness ratios to rule out gender influence did not show any different results for the 3 locations. Censoring of the minor individuals did not change any results.

To compare the disease progression throughout life at various anatomical locations scatterplots with outcome values versus age to compare groups 1 and 3 (Figure 5.4). There is frontal, parietal and occipital skull thickening throughout life in the affected group. Whereas inner table thickening is mainly responsible for this in the frontal bone, in the parietal bone there is mainly thickening of the diploë (the inner and outer table are stable throughout life, Figure 5.4B). In the occipital bone there is thickening of all three layers. The middle and frontal skull base show progressive hyperostosis, in contrast to the clivus and foramen magnum (Figure 5.4D). Narrowing of the porus region of the internal auditory canal is one of the first pathologic changes to occur. No decline in group 1 porus width is visualised, because the youngest subjects already have a markedly narrowed porus (less than 1.5 mm). Fundus narrowing continues until later in life and is observed to a lesser extent in the control population as well.

Table 5.2 Overview of different distance measurements.

Location	Normal distribution +/-	Group 1 Fam + HCI +		Group 3 Controls matched with group 1		Group 2 Fam + HCI -		Group 4 Controls matched with group 2	
		Mean (mm)	SD	Mean (mm)	SD	Mean (mm)	SD	Mean (mm)	SD
Frontal Total	+	11.2 ††	3.2	5.9 ††	1.4	5.6	1.4	5.5	1.8
Frontal Inner table	-	3.2 ††	1.8	1.2 ††	0.7	1.5 ‡	0.4	1.1 ‡	0.4
Frontal Outer table	+	2.0 ††	0.5	1.1 ††	0.3	1.6 ‡†	0.4	1.1 ‡†	0.5
Parietal Total	-	9.4 ††	3.7	2.2 ††	1.1	2.8	0.7	2.4	1.1
Parietal Inner table	+	1.7	1.0	1.1	0.4	1.5	0.4	0.8	0.4
Parietal Outer table	+	1.9 †	0.6	1.0 †	0.4	1.4	0.5	1.2	0.7
Occipital Total	+	7.6 ††	2.1	4.9 ††	1.5	5.6	1.2	5.0	2.0
Occipital Inner table	+	1.9 †	0.9	0.9 †	0.2	1.2 ‡	0.3	0.9 ‡	0.3
Occipital Outer table	+	2.4	0.8	2.0	0.5	1.7	0.5	1.6	0.6
Frontal Skull base	-	2.9 ††	2.0	0.8 ††	0.1	1.6 ‡†	0.6	0.8 ‡†	0.2
Middle Skull base	-	4.3 ††	1.9	0.7 ††	0.1	1.3 ‡†	0.4	0.6 ‡†	0.1
Foramen magnum	+	1.9 ††	0.3	1.3 ††	0.4	1.8 ‡†	0.4	1.2 ‡†	0.2
Clivus Inner table	+	1.1	0.4	0.8	0.2	1.2 ‡†	0.3	0.8 ‡†	0.3
Porus IAC	-	1.1 ††	0.4	4.1 ††	0.6	4.0	0.7	4.3	0.8
Fundus IAC	+	2.8 ††	1.1	5.3 ††	1.0	5.1	0.5	5.1	0.7
Optic canal	+	3.7	1.6	4.2	0.8	4.1	0.5	4.0	0.8
Vidian canal	+	1.0	0.5	0.9	0.3	1.2	0.4	1.0	0.3
Coronoid suture	+	4.6 †	1.2	3.0 †	0.9	2.7	1.7	4.0	1.5
Lambdoid suture	+	7.0 ††	2.4	4.0 ††	1.4	3.9	1.5	4.5	1.6

† paired T-test 1-3 $p \leq 0.05$ ‡ paired T-test 2-4 $p \leq 0.05$ †† paired T-test 2-4 $p \leq 0.005$ ‡† paired T-test 2-4 $p \leq 0.005$

Density measurements

The assumption of normality could be made for all density measurements so that the paired sample *t* test could be applied. For general measurements (frontal, parietal, occipital, and petrous bone, and greater wing of the sphenoid bone) there were no significant differences between group 1 and 3 or between group 2 and 4. Groups 2, 3, and 4 display a trend of gradually decreasing density values throughout life, as expected in normal bone tissue⁵.

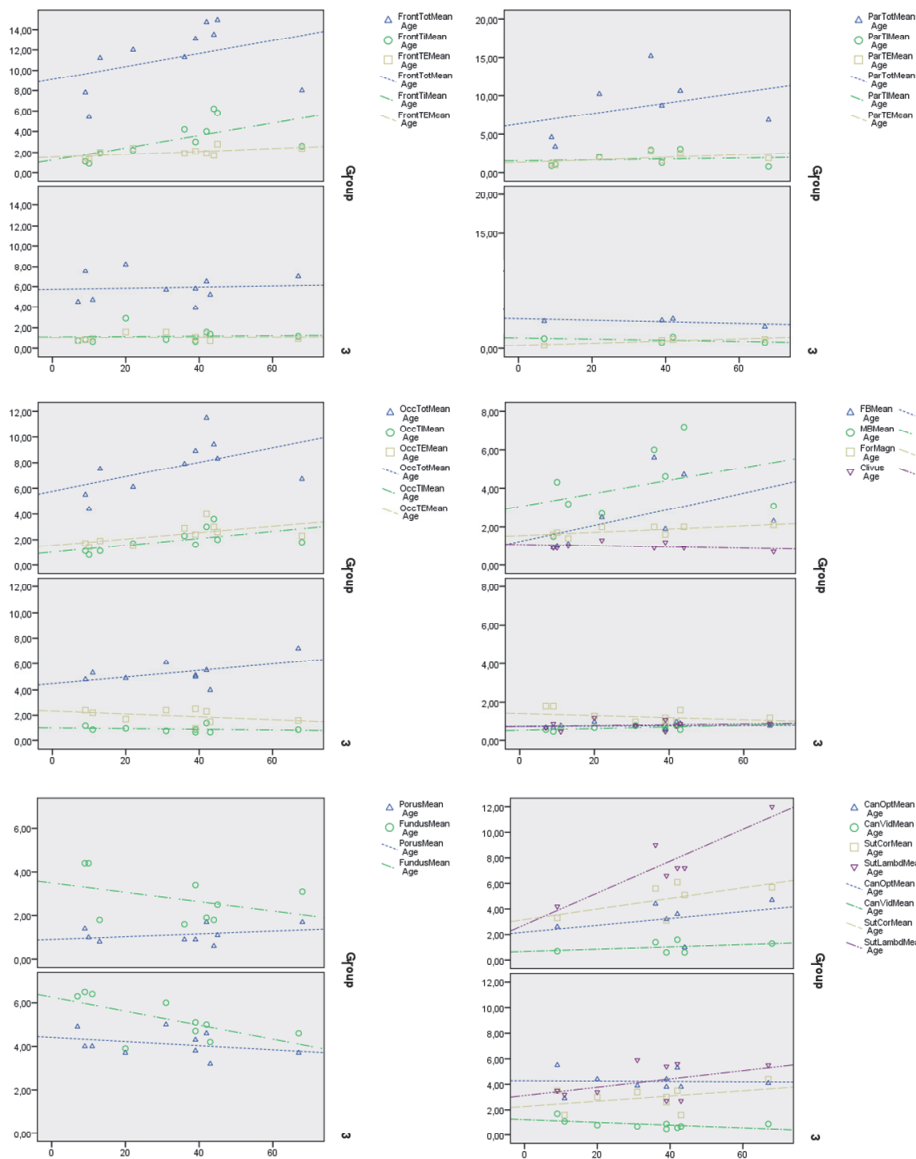


Figure 5.4 Evolution of groups 1 and 3 per anatomic region. A: frontal bone, B: parietal bone, C: occipital bone, D: skull base, E: internal auditory canal and F: miscellaneous. X-axis = age, Y-axis = distance (mm). TI = inner table (tabula interna), TE = outer table (tabula externa).

Significantly lower densities were found in group 1 in all *inner table* areas: greater sphenoid wing, frontal bone, parietal bone and occipital bone compared with group 3 (Table 5.3). No differences were found in any trabecular/medullar bone areas. No

statistical differences were found in outer table areas, although affected individuals tended to have denser outer table bone than unaffected individuals. Inner table density measurements are lower in affected individuals than outer table density, in contrast to unaffected individuals (Figure 5.5). Skull sutures in affected individuals generally have a lower density than control subjects.

Table 5.3 Specific density measurements.

Location affected group 1 – Reference location matched group 3	Mean density group 1 – Mean density group 3 (HU)	Mean 1-3 (HU)	SD	Paired t test (p)
Sphenoid Inner table 1	1022.6			
Sphenoid Inner table 3	1382.1	-359.5	231.8	0.001
Sphenoid Diploë 1	115.5			
Sphenoid Diploë 3	138.6	-23.1	92.0	0.448
Frontal Inner table 1	1191.9			
Frontal Inner table 3	1350.6	-158.8	60.2	0.000
Frontal Diploë 1	427.8			
Frontal Diploë 3	325.7	102.1	176.8	0.101
Frontal Outer table 1	1489.4			
Frontal Outer table 3	1347.6	141.8	199.4	0.084
Parietal Inner table 1	1115.0			
Frontal Inner table 3*	1350.6	-235.6	196.1	0.011
Parietal Diploë 1 *	397.2			
Frontal Diploë 3	334.0	63.2	250.0	0.470
Parietal Outer table 1	1442.5			
Frontal Outer table 3	1347.6	94.9	149.0	0.115
Occipital Inner table 1*	1136.8			
Frontal Inner table 3	1353.4	-216.6	82.0	0.000
Clivus 1	235.6			
Clivus 3	204.6	31.0	110.2	0.397
Sphenopetrosal suture 1	1176.2			
Sphenopetrosal suture 3	1206.7	-30.5	186.6	0.618
Tympanosquamosal suture 1	1393.8			
Tympanosquamosal suture 3	1484.3	-90.5	86.9	0.009
Medulla lateral orbita 1	271.1			
Medulla lateral orbita 3	265.3	5.8	128.3	0.889
Exostoses mandible 1	1340.0	N/A	86.0	N/A

Comparison of bone density of specific location between group 1 and 3. Areas indicated with * in group 3 were too small to be measured separately. Therefore, the frontal area was used as reference.

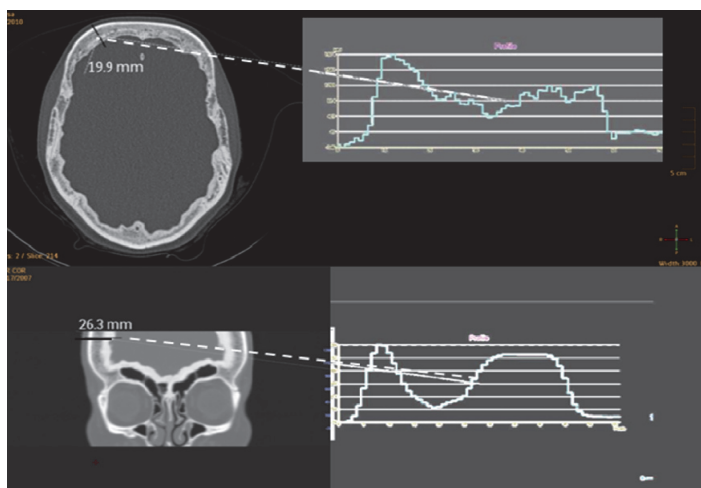


Figure 5.5 Density profiles of skull transections in frontal (upper) and frontotemporal (lower) bone (upper) region. X-axis: distance, Y-axis: density (HU). The higher peak correlates with the outer table. Inner table density measurements are found to be lower in affected individuals than outer table density, in contrast to unaffected individuals.

Descriptive analysis per affected region

Frontal bone, frontal sinus & anterior skull base

Late in the first decade, radiological abnormalities become visible in the frontal bone. The first changes are small hypodense islands in the medulla, both medial as well as lateral toward the temporal line (Figure 5.6). These expand towards the outer table in a balloon-like manner, accompanied with a general thickening of the diploë. Then, focal hyperdense sclerotic spots arise at the border of inner table and the inner diploë initially without significant thickening of the inner table. In puberty, the hyperdense spots merge and circularly augment from the inner table inward, resembling tree rings. The inner border of the significantly thickened diploë stays hypodense at the border with the enlarging inner table. The sclerotic circular layers of hyperdense augment gradually and fuse in the second or third decade. The inner surface becomes more rugose, and from the fourth decade on there is generally no more significant growth.

Pneumatisation of the frontal sinus occurs earlier and is more extensive than average. The inner table of the frontal sinus, as well as the internal frontal beak (inner aspect of the glabella/nasofrontal area) display hyperostotic changes late in the second decade. There is limited thickening of the outer table at the level of the sinus and the frontal bone as well.

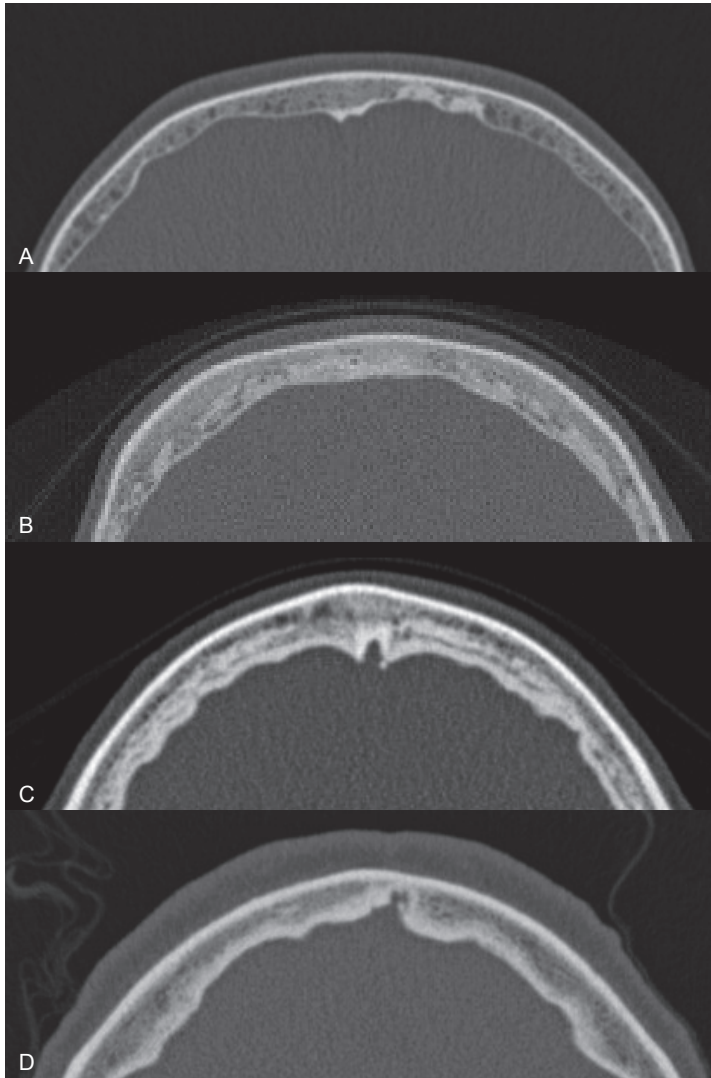


Figure 5.6 Development of abnormalities in the frontal bone, axial images. A: age 9. B: age 16. C: age 23 and D: age 68.

Parietal & temporal bones

Abnormalities in the parietal bone start off as early as in the frontal bone. Hypodense areas arise at the endosteal side of the diploë from the age of 8. Initially, only the diploë grows thicker and the inner surface becomes irregular, without obvious thickening of the inner table. The petrosquamous suture lines become sclerotic, in this

area the three bone layers (inner table, outer table and diploë) cannot not be differentiated. In the second and third decade there is further thickening of the diploë and hyperostosis of the inner table becomes apparent. The same pattern as in the frontal bone is observed: a hypodense demarcation between inner table and diploë. In contrary to the frontal bone, the hyperostotic layer does not have a circularly layered aspect. From this age, disease progression is variable per individual.

The temporal bone (Figure 5.7) is generally extensively pneumatised, also towards the petrous apex and the zygomatic root. The first temporal bone abnormalities are visible by the age of 10. The lateral mastoid, just cranial to the external ear canal has a sclerotic aspect in all individuals, seemingly a sclerotic petrosquamous suture. In the second decade the sclerosis of the petrosquamous suture (or Körner's septum in the mastoid) expands, causing obliteration of the lateral mastoid and air cells around the zygomatic root.

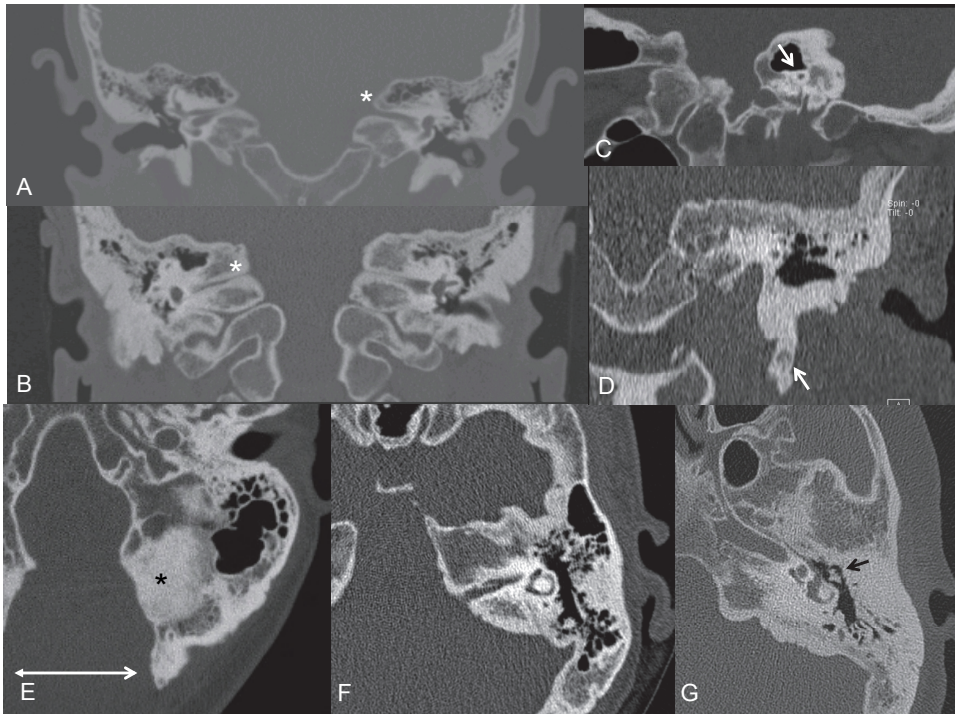


Figure 5.7 Temporal bone. A: 9-year-old boy. Hyperostotic superior (asterisk) and inferior lip of the internal auditory canal (coronal reconstruction). B: 41-year-old female. Pinpoint internal auditory canal (arrow, sagittal reconstruction). C: Progressive bilateral narrowing of the IAC in a 16-year-old girl (asterisk, coronal reconstruction). D: hyperostotic stylomastoid process in a 44-year-old woman (arrow, coronal reconstruction). E-G: axial images of left temporal bones with extensive hyperostosis in posterior fossa (asterisk) after foramen magnum decompression (double-headed arrow) (E, 41-year-old woman), extensive pneumatization progressively substituted by sclerotic bone (F and G). Note the middle ear space is not affected (arrow G).

Endosteal thickening of the temporal bone starts at the posterior aspect and the internal auditory canal region in the late first or early second decade, first as small hyperdense speckles. A clear endosteal hyperostotic margin becomes visible later in the second decade, now also including the anterior and superior aspect of the petrous bone.

Internal auditory canal narrowing is invariably visible at the level of the porus in the late first decade. The petrous apex, even when initially pneumatized, becomes sclerotic. There is thickening of both the inferior and superior lip of the canal; however, bone accretion of the superior lip seems to contribute most of the narrowing. The canal size decreases until a pinpoint lumen (0.5-1 mm)⁶.

The sclerotic stylomastoid process becomes hyperostotic and sclerotic in older individuals as well.

Sphenoid and ethmoid bones

The endocranial side of the greater sphenoid wing displays the same abnormalities as the frontal bone: hypodense areas of the diploë and sclerotic endosteal foci appearing late in the first decade. Fusion sites with other adjacent osseous structures have a sclerotic aspect as well: the sphenosquamous suture (connection with temporal bone), sphenofrontal suture, and sphenozygomatic sutures. Fusion with the clivus is not yet established at this age. The lamina cribrosa and the ethmoid cells are, as yet, unaffected. The anterior midline aspect of the sphenoid bone, the jugum, or corpus sphenoidale facing the ethmoid sinuses becomes sclerotic even before the sphenoid sinus is fully pneumatized. When the sphenoid sinus is developed, the anterolateral wall of the sinus becomes more explicitly thickened than in unaffected individuals. In the second decade this hyperostosis becomes more evident and the (anterior portion of the) lamina papyracea becomes involved as well. The clivus fuses with the sphenoid bone without any evident sclerosis at this fusion site. Until the mid-20s, there is significant progression of disease at the endocranial side of the greater and lesser sphenoid wing (Figure 5.8A). The sclerotic endosteal borders transform into a well-defined hyperdense hyperostotic bone layer, which becomes continuous with the parietal and petrous bone. Remarkably, the endocranial side of the corpus of the sphenoid and the tuberculum sellae are spared.

If an individual is severely affected the patency of the superior orbital fissure is potentially compromised due to hyperostosis of both the superior aspect of the greater sphenoid and the inferior aspect of the lesser sphenoid wing. The patency of the optic canal is specifically at risk at the narrowest part where hyperostosis of the superolateral aspect of the sphenoid sinus and hyperostosis of the medial side of the lesser sphenoid wing occur (Figure 5.8D).

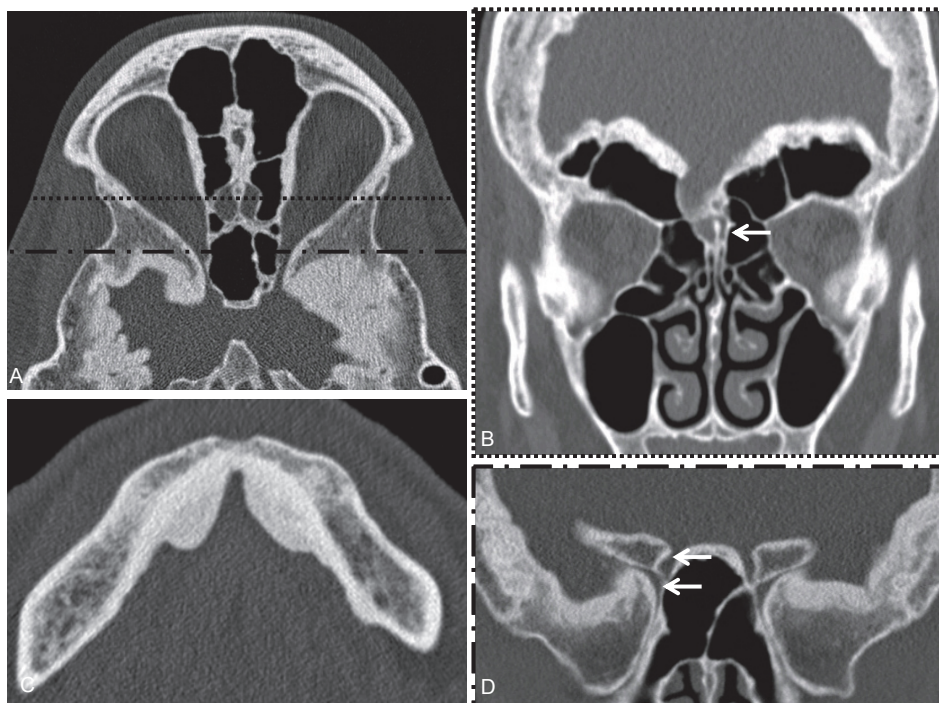


Figure 5.8 Sphenoid, ethmoid, mandible. A: axial image of 23-year-old woman. Hyperostosis of endosteal greater sphenoid wing, decreased space in temporal lobe area. Hyperostotic lamina papyracea and lamina cribrosa area. Anterior line corresponds with coronal image B (different patient), posterior line corresponds with the coronal image D (same patient). B: coronal image of 41-year-old woman showing extensive supraorbital pneumatisation and inclusion of unaffected crista galli (arrow). C: axial image of mandibular exostoses in a 68-year-old patient. Note that the inner table of the mandible has a normal aspect. D: coronal image (same patient as A) of the greater and lesser sphenoid wings. Note narrowing of the optic canal (upper arrow) and the superior orbital fissure (lower arrow).

Middle and posterior skull base

Symptomatology of neural and vascular structures passing the various middle skull base neuroforamina is dependent on the degree of encroachment. The foramen rotundum and ovale can be narrowed in their proximal part, leading to dysfunction of the second and third branches of the trigeminal nerve in severely affected individuals. The Vidian nerve and pterygopalatine fossa are never narrowed. The carotid canal is not affected at all whereas asymptomatic sigmoid sinus narrowing is present in individuals with extensive posterior fossa hyperostosis. The jugular foramen is not narrowed. The foramen spinosum and hypoglossal canal are patent in all patients.

Skull sutures

Skull sutures are affected to a various extent from late childhood. There is explicitly no endosteal hyperostosis at the fusion sites, however osteosclerosis occurs parallel to the suture in the direction of the connecting plates.

Mandible

Changes occur to the mandible later in life (Figure 5.8C). There is smooth delineated ellipsoid deposition of bone at the inner (oral) side of the anterior half of the mandible, sparing the midline. The density is lower than cortical bone, similar to the cranial abnormalities. This is only observed from the age of 36 onward. Unlike abnormalities of the frontal region and the skull base region, the otherwise intact inner cortex can still be differentiated from the disease-related bone deposition.

Discussion

In HCI, endosteal hyperostosis occurs in the parietal, the frontal, the occipital, the sphenoid, the ethmoid and the temporal bones, without obliteration of the diploë. The most marked change is thickening of the inner table of the calvaria, except for the parietal region, where broadening of the diploë is more explicit. The reason for this difference is unclear. The appearance of the outer table of the patient group is not disturbed, but is slightly thickened in the adult affected individuals. The cranial nerve deficits are caused by hyperostosis of the skull base. Furthermore, skull sutures become more sclerotic than in unaffected individuals, and the lateral parts of the mastoids and the petrous apices undergo sclerotic changes. The stylo mastoid process is affected showing broadening and exostoses. All patients develop mandibular exostoses at the interior surface of the anterior half of the mandible at a later age. Clinically and upon descriptive radiologic examination, female patients are more severely affected than male. There is no statistical support for this phenomenon. The diploë never obliterates because the bone accretion seems to take place at the endosteal side of a hypodense circular “front”, with ballooning spongy spots in the diploë and net bone growth follows an inward (endosteal) direction. In similar sclerosing bone dysplasias, like Camurati-Engelmann disease, Van Buchem disease and sclerosteosis there is obliteration of the diploë. However, whether this bone accretion actually takes place at the outside of the inner table or at the inside of the diploë can only be proven histologically.

The outcome of the analyses of the internal auditory canal confirm the management as has earlier been proposed by our group. Narrowing of the porus occurs at a very young age to a size that causes dysfunction of the facial and vestibulocochlear nerves in

almost all patients. Early intervention (decompression) is advised⁶. The fundus narrows gradually at a later age (down to 2 mm), just as it does in the normal population (4mm). For the optic system it is harder to arrive at a straightforward conclusion. Although there is no statistically significant difference between the width of the optic canal in affected and unaffected individuals, the difference is apparent with a greater individual variation as seen in the larger standard deviation. Impairment of the optic nerve, if any, occurs at the narrowest point of the optic canal, due to hyperostosis of the medial *lesser* sphenoid wing, as depicted in Figure 5.8A and 5.8D. Another plausible option could be impairment of venous outflow of the ophthalmic vein due to a narrowed superior orbital fissure (due to hyperostosis of the medial *greater* sphenoid wing, Figure 5.8D).

Paranasal sinus and petrous bone pneumatisation is remarkably extensive in all young patients, however this could be a non-disease-specific coincidental finding (fig. 9B). The young affected individuals have a fully developed frontal sinus at the age of 7, whereas normally the sinus does not appear before this age. The early extensive petrous bone pneumatisation is generally replaced by secondary sclerosis.

In the available literature little is found about reference values of bone density in the skull. In oral implantologic studies have been performed to optimise implant osseointegration by correlating the density to the bone strength. Misch *et al.* have proposed the following classification: dense cortical (D1, >1250 HU), porous cortical (D2, 850-1250 HU), coarse trabecular (D3, 350-850 HU) and fine trabecular bone (D4, <400 HU)⁷. The hyperostotic bone in HCI has the appearance and also the densitometric characteristics of porous cortical bone (D2), resembling the density of abnormalities in Paget's disease and fibrous dysplasia.

The outer table of the patient's calvaria have similar density values as the unaffected population and the control patients. The trabecular bone (diploë) at different sites of patients is similar to mandibular trabecular bone as described in oral implantology literature (240-380 HU)⁸. The density degradation can be compared to the process that is visible in otosclerosis, where dense (D1) cortical bone of the otic pit is transformed into porous cortical bone containing more fibrous and less calcified tissue^{9,10}.

There is not yet a definite explanation why some particular areas are involved and others not. Given the fact that only the craniofacial area is involved, there must be a local factor that causes bone metabolic disturbance. The inward (endosteal) hyperostosis pleads for a potential role of the dura mater, which is known to produce signalling substances involved in bone metabolic pathways¹¹. However, not all structures adjacent to dura are affected equally: the occipital area is less affected than the temporal area, there is hardly any hyperostosis in the area of the clivus and foramen magnum and the spine is not affected at all. Besides, the stylomastoid process

and the mandible display abnormalities, not being adjacent to dura. The course of the disease could also give a clue about the pathogenesis. Abnormalities are not seen before the late first decade. If regional (dural) factors do induce abnormal growth, different gene expression in juvenile and in adult dura possibly explain why abnormal growth does not occur in all stages of life¹². Different cellular pathways are described that control the growth pace of the skull and the appropriate timing of skull suture closure¹³. Defects in one of these mechanisms occur in disorders in the group of craniosynostoses (e.g. Crouzon and Apert syndromes) as well⁴.

Although the genetic transmission pattern is clearly autosomal dominant and “unaffected family members” obviously have no abnormal radiological hallmarks and no symptomatology, there are some significant differences in contrast to their control group. This reminds of incomplete dominance, however this can only be proven after the detection of the underlying genetic defect.

Conclusion

Hyperostosis cranialis interna is a bone dysplasia with abnormalities limited to the craniofacial area. The hyperostotic bone is less dense than normal cortical bone. The observed radiological abnormalities match the possible impairment of the olfactory, optic, trigeminal, facial and vestibulocochlear nerves. The pathogenesis remains obscure until the underlying genetic defect is found, but disturbance in local bone metabolic pathways appear to be involved.

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Chapter 6

Bone metabolic activity in hyperostosis cranialis interna measured with ^{18}F -fluoride PET

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Abstract

Introduction

^{18}F -fluoride PET/CT is a relatively undervalued diagnostic test to measure bone metabolism in bone diseases. Hyperostosis Cranialis Interna (HCI) is a (hereditary) bone disease characterised by endosteal hyperostosis and osteosclerosis of the skull and the skull base. Bone overgrowth causes entrapment and dysfunction of several cranial nerves. The aim of this study is to compare standardised uptake values (SUVs) at different sites in order to quantify bone metabolism in the affected anatomic regions in HCI patients.

Methods

Nine affected family members, 7 non-affected family members and 9 non-HCI-non-family members underwent ^{18}F -fluoride PET/CT scans. SUVs were systematically measured in the different regions of interest: frontal bone, sphenoid bone, petrous bone and clivus. Moreover the average ^{18}F -fluoride uptake in the entire skull was measured by assessing the uptake in axial slides. Visual assessment of the PET scans of affected individuals was performed to discover the process of disturbed bone metabolism in HCI.

Results

^{18}F -fluoride uptake is statistically significant higher in the sphenoid bone and clivus regions of affected family members. Visual assessment of the scans of HCI patients is relevant in detecting disease severity and the pattern of disturbed bone metabolism throughout life.

Conclusion

^{18}F -fluoride PET/CT is useful in quantifying the metabolic activity in HCI and provides information about the process of disturbed bone metabolism in this specific disorder. Limitations are a narrow window between normal and pathologic activity and the influence of age. This study emphasises that ^{18}F -fluoride PET/CT may also be a promising diagnostic tool for other metabolic bone disorders, even those with an indolent course.

Introduction

Hyperostosis cranialis interna (HCI) (OMIM 144755) is a disorder which was first described in 1990 and is characterised by hyperostosis and osteosclerosis of the calvaria and skull base (Figure 6.1)¹.

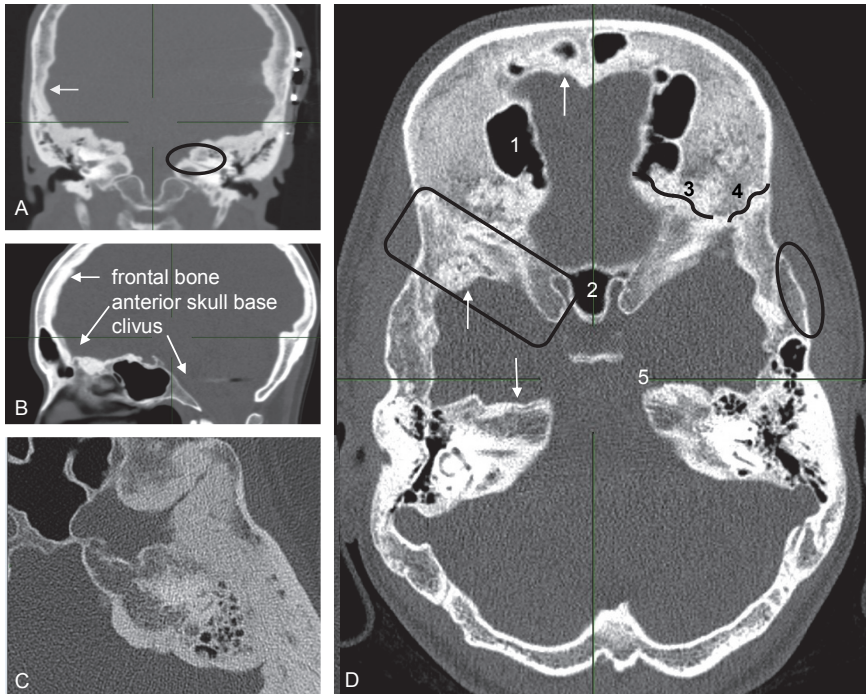


Figure 6.1 CT Images of affected individuals. (A) Coronal reconstruction of the middle skull base with near-total obliteration of the internal auditory canal (oval), endosteally thickened parietal area (arrow). Note the subcutaneous wires of auditory brainstem implantation (left). (B) Paramedian sagittal reconstruction. Frontal bone and anterior skull base are moderately affected. Vertebral column, nasal bones and clivus show no hyperostosis. (C) Axial image of the temporoparietal area revealing exorbitant endosteal hyperostosis. (D) Axial overview of a 24-year-old affected woman: 1. right frontal sinus 2. sphenoid sinus 3. sphenofrontal suture 4. sphenoparietal suture 5. apex of the petrous bone. Arrows: apposition of excessive endosteal bone. Oval: normal configuration of outer cortex. Square: greater sphenoid wing.

This leads to a narrowing of cranial nerve foramina causing entrapment and dysfunction of cranial nerves I, II, V, VII and VIII. Facial palsy and vestibulocochlear dysfunction occur at young age, mainly in the second and third decades. Smell and vision impairment and trigeminal neuralgia may occur later. It is a hereditary disorder that, to date, has been diagnosed in three related Dutch families only². Besides HCI,

numerous bone dysplasias with skull base and calvarial hyperostosis and osteosclerosis exist. Van Buchem disease^{3,4}, Camurati-Engelmann disease⁵ and sclerosteosis⁶ are examples of similar disorders with increased bone density, however with metaphyseal and/or diaphyseal involvement. An overview of different (genetic) skeletal disorders is provided by the International Skeletal Dysplasia Society⁷. HCl and X-linked calvarial hyperostosis are the only bone disorders affecting solely the skull.

The diagnosis HCl is suspected by family history and physical examination and confirmed by computed tomography (CT). Analysis of sequential CT scans of affected individuals gives the impression that the frontal bone and the (medial part of the) petrous bone are affected first, in the late first or early second decade. This process seems to continue until the age of 40. In the greater sphenoid wing hyperdense areas are visible in adolescence (comparable to the frontal bone region), however usually obvious hyperostosis starts later (3rd decade) and progresses until later in life. Findings for the parietal bone are similar, becoming pathologically dense and hyperostotic from the 3rd decade on. The anterior and middle skull base are affected, whereas the occipital region is hardly involved (Figure 6.1). In HCl there is no involvement of the tubular bones. An additional dynamic bone imaging technique, ¹⁸F-fluoride Positron-Emission Tomography (PET), could provide valuable information in analysing and quantifying bone metabolism.

¹⁸F-fluoride was described as a tracer for bone imaging by Blau *et al.* in 1962 and 1972 (conventional scintigraphy), but fell into disuse^{8,9}. In 1992, PET scans using ¹⁸F-fluoride were introduced to quantify bone formation¹⁰. Compared to conventional gamma cameras including SPECT, PET scans have higher spatial resolution and a greater sensitivity than gamma cameras and offer direct quantification of bone imaging studies. Grant *et al.* reviewed the available studies about clinical utility of ¹⁸F-fluoride PET/CT scanning¹¹. Although the specific bone uptake is similar for both radionuclides, there is less plasma protein-binding of ¹⁸F-fluoride¹² and the half-life is considerably shorter (110 minutes and 6 hours respectively). ¹⁸F-fluoride PET scanning offers shorter study times and is therefore more convenient for patient and physician. The effective dose of ¹⁸F-fluoride PET is somewhat higher compared to ^{99m}Tc bone scanning (4.0 versus 3.0 mSv resp.)¹¹. ¹⁸F-fluoride PET is more accurate than planar imaging or SPECT with ^{99m}Tc-MDP for the detection of small focal lesions, such as metastases¹³. Because of its easier quantification capabilities, ¹⁸F-fluoride is very useful for the assessment of bone metabolism.

With ¹⁸F-fluoride PET differences in bone metabolism between affected HCl patients, unaffected family members and unaffected control subjects are visualised and quantified in different anatomic subsites. The aims of this study are 1. to provide additional information about the early stage of HCl and, 2. to monitor disease activity at different anatomic subsites and predict disease progression which can be important for treatment decisions.

Materials and methods

Subjects

The 3 related families have common progenitors and consist of 31 individuals (Figure 6.2), 3 of whom have deceased. One individual did not participate because of a psychiatric condition at the time of the study. A total of 11 children (all under 5 years old) did not undergo a PET/CT scan because of their age. The remaining 16 were included: 9 family members with proven CT abnormalities (group 1) and 7 family members without CT abnormalities (group 2).

The control group consisted of 9 patients (group 3), mainly examined for orthopaedic diagnostic reasons (without symptoms or a disease history in the head and neck region). The medical ethics committee of the Maastricht University Medical Centre approved the research protocol (document number MUMC 09-4-050.4/PL) and all patients gave their written informed consent. All individuals underwent a ¹⁸F-fluoride PET/CT scan between August 2007 and November 2008.

PET imaging

The average ¹⁸F-fluoride activity administered to all patients was approximately 200 MBq (effective dose 5.4 mSv). PET/CT scans of the head and upper torso were made after 1 hour, acquiring data for 4 min per bed position. A PET/CT scanner with a 64-slice CT component (Gemini TF; Philips, Best, The Netherlands) was used. In all cases, low-dose CT (30 mAs, 0.5 mSv) was performed. If needed for diagnostic reasons, high-resolution CT was performed as well. Using the standard Philips time-of-flight ordered subsets expectation maximisation reconstruction (33 subsets, 3 iterations), images corrected for random events, scattered radiation, and attenuation were obtained. The PET matrix size was 144, resulting in a voxel size of 4 x 4 x 4 mm³.

Visual assessment

All PET scans were visually analysed and compared to the complementary CT scans with Philips Extended Brilliance™ Workspace in order to assess their clinical value. This program is used for assessment of PET/CT scans in everyday clinical practice at our institute. The PET scans were fused with the 4 mm CT scans and depicted in “thermal” colour scale setting and compared to high-resolution CT scans of the skull base. The areas of interest were analysed by displaying identical settings: the low-level filter was set at standardised uptake value (SUV)=1.3, the upper-level filter at SUV=12.0. Additionally, hot spots were detected by visual scoring of the scans and by assessing the SUV_{max} of each slice.

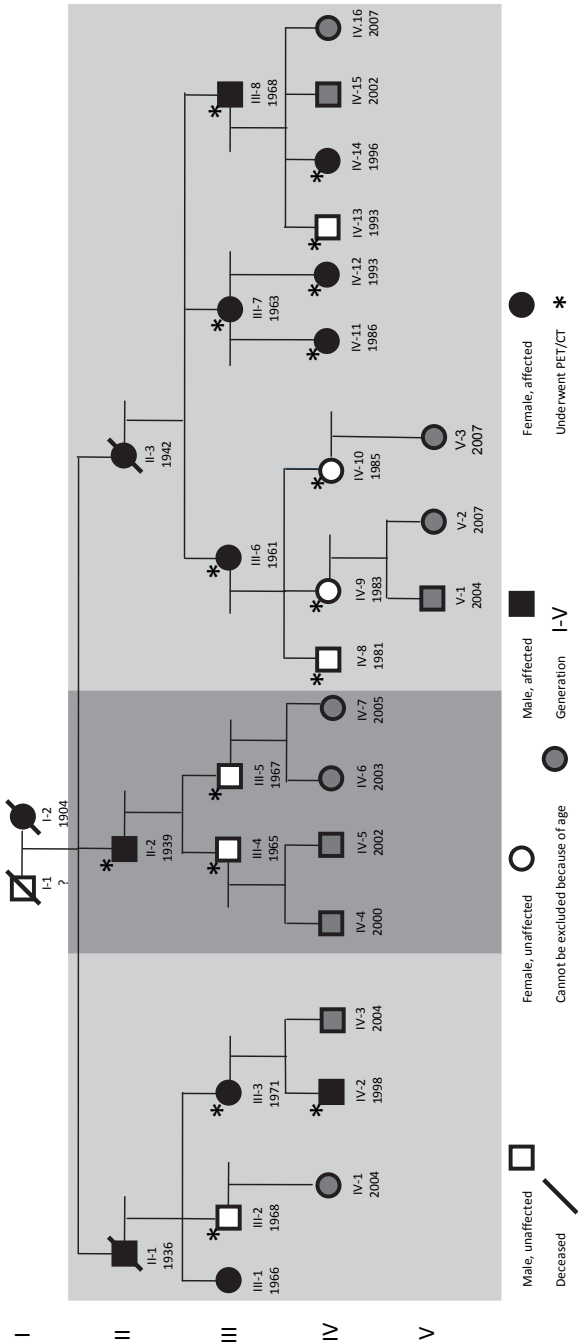


Figure 6.2 Pedigree of the affected HQL families.

Standardised measurements

The scans were analysed using PMOD 2.95 (PMOD Technologies Ltd., Zurich, Switzerland). A region of interest (ROI) with a radius of 5 mm was placed in the axial plane around the maximal activity in different anatomical regions: greater sphenoid wing (left and right), frontal bone (cranial to orbita or frontal sinus), apex of the petrous bone (left and right) and clivus. First, in each of these anatomical regions a manually drawn ROI was created including the entire region. This was repeated for all planes comprising the concerning region and in these ROIs the point of maximal activity was assessed. Consequently, the coordinates of these points of maximal activity were used as the centre of the smaller, circular ROIs with a radius of 5 mm. The data of this ROI were used for calculation of the SUV. For all anatomic subsites the SUV_{mean} and SUV_{max} were calculated.

The corpus of the third cervical vertebra was chosen as internal control site. In the area scanned, the vertebrae, clavicles and the cheek bones are the only bony structures clearly not affected in HCI-patients. The vertebrae were considered the most appropriate because of their size. None of the scanned individuals, regardless of group, had neck conditions.

Total uptake of the skull was also assessed. ROIs were created in the axial plane with the inside (A) and outside (B) boundaries of the skull (Figure 6.3). The uptake in the bone was drawn up by subtracting the data of A from B. Next we calculated the average uptake in the entire skull. To accomplish this the average uptake in all planes (from the skull base to the vertex) were added and divided by the total volume (slice thickness of 1 region equals 4 mm). With these data the SUVs of the ROIs were calculated using the following formula:

$$SUV[g/ml] = \frac{TissueActivity(kBq/ml)}{ActivityInjectedDose(kBq)/BodyWeight(g)}$$

Statistical analysis

Sample means, standard deviations and the range of SUV_{mean} and SUV_{max} were calculated per group. Kolmogorov-Smirnov tests were performed for all continuous metric data to test for normality. Frequencies and percentages are given for categorical data.

Both the parametric analysis of variance (ANOVA) and the nonparametric Kruskal-Wallis overall tests were performed to examine differences between the three groups. To compare HCI patients and non-HCI family members on the one hand and HCI patients and control subjects on the other hand, the parametric *t* test and the Mann-Whitney test were used.

All data were analysed with SPSS PC version 16; *p* values less than 0.05 were considered as denoting statistical significance.

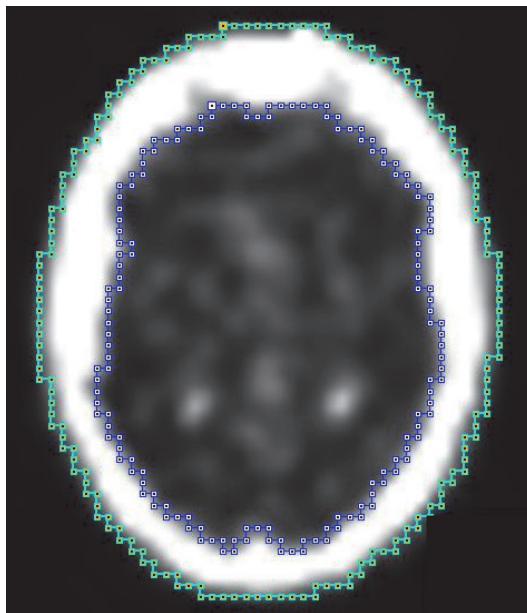


Figure 6.3 Measuring the total uptake of the skull using PMOD 2.95: A (inside) = inner dotted line, B (outside) = outer dotted line; total skull uptake per slice was calculated by subtracting the data of A from B (B-A). Results of all planes together (up from the skull base to the vertex) were added resulting in the total uptake of the bone.

Results

In group 1, 9 (affected) individuals were included (6 women and 3 men; mean age 32; range 11-68). Group 2 consisted of 7 non-HCI family members (5 women and 2 men; mean age 29; range 14-40). A total of 9 control subjects (group 3) were scanned (5 women and 4 men; mean age 60; range 42-75).

Visual assessment

General findings

Skull sutures show enhanced uptake in all individuals, both affected as well as unaffected. In unaffected individuals minor physiological irregularities are sometimes observed at the endosteal side of the frontal bone area on CT as well. However, other parts of the cranial vault are always smoothly delineated in unaffected individuals. Hot spots unrelated to HCI (Figure 6.4) are for example areas of embryologically fused bone (i.e. clivus, sphenoid wing), the nasal bones and the temporomandibular joint.

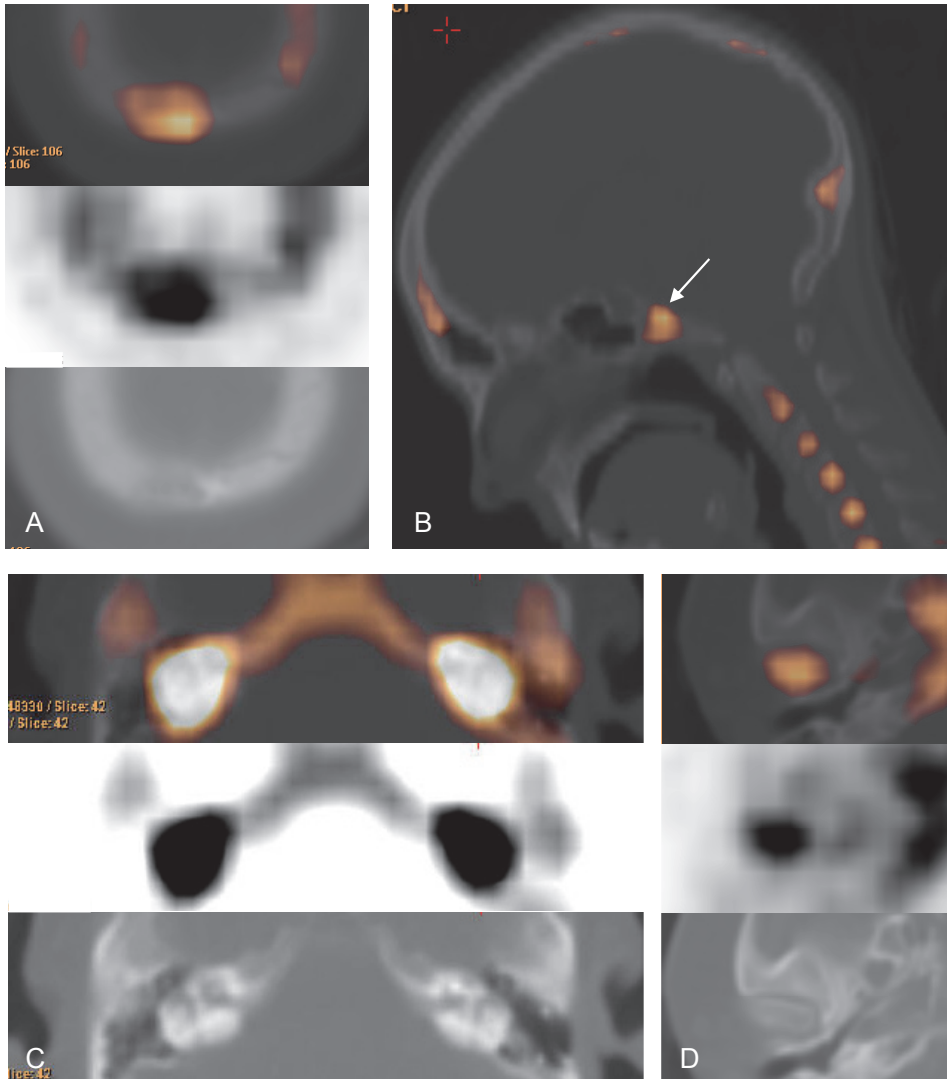


Figure 6.4 Hotspots unrelated to HCI. First of paired images is fused PET/CT, second PET, third CT alone. (A) Occipital osteoma cranial to foramen magnum. (B) Hotspots visible in metabolically active bone regions. Note the clivus (arrow), which is a junction of two bone segments. The centre of the corpora of the vertebral column and the occipital protuberance show enhanced activity as well. (C) Bilateral enhancement of the labyrinth in a control subject with cochlear otosclerosis. (D) Hotspot at the caput mandibulae/ temporomandibular joint.

Hotspots and other interesting findings related to HCI are displayed in Figure 6.5. The majority of the hot spots (besides those found in the standardised measurement areas) are found in three different regions: the cranial part of frontal bone, the sphenofrontal suture and the occipital suture.

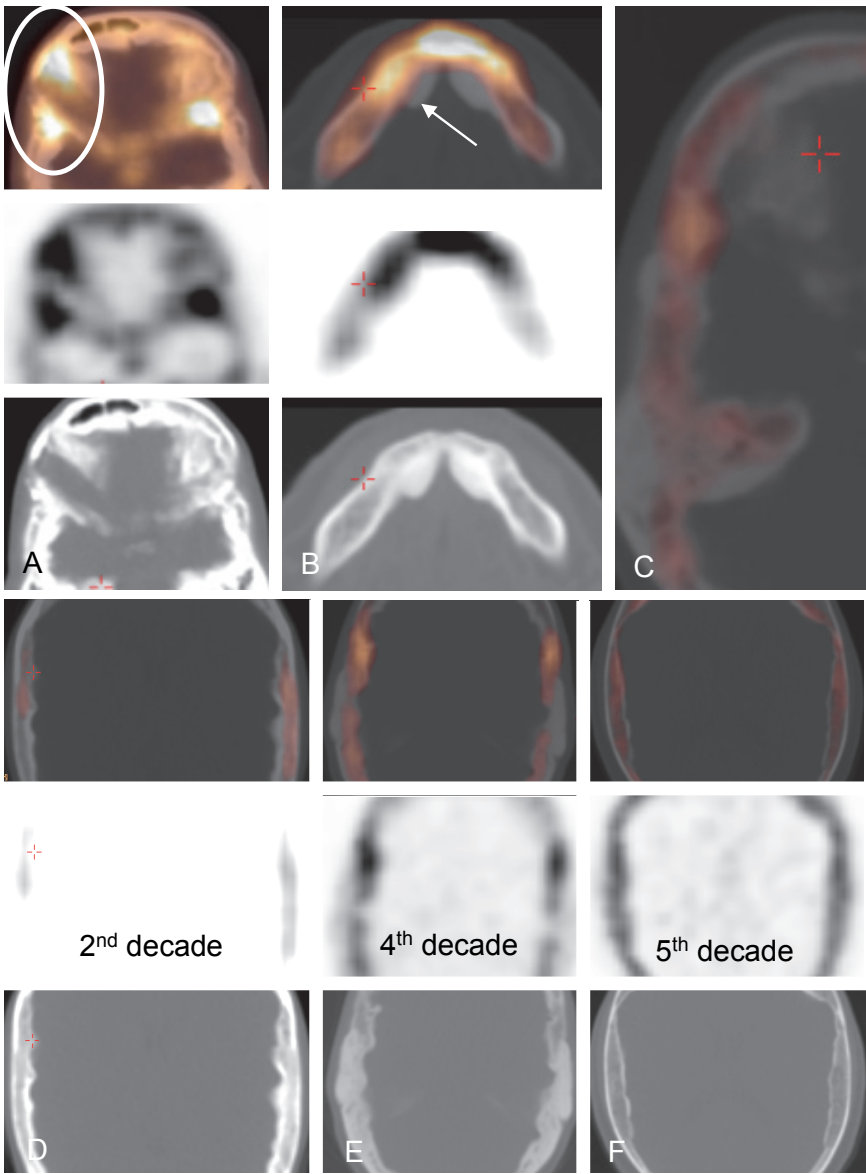


Figure 6.5 Hotspots and other findings in HCI-affected individuals. First of paired images is fused PET/CT, second PET, third CT alone. (A) Postoperative status after optic nerve decompression at the right side in an affected individual. The oblique operation tract can still be seen (oval). Hotspot at the junction between the greater sphenoid wing, the frontal bone and the parietal bone at the left side. (B) Hotspot at the symphysis mandibulae. Typically the mandibular exostoses (arrow) do not show enhanced uptake; the symphysis mandibulae and the base of the exostoses do have enhanced uptake. (C) View of the whole right axial skull base of a 39-year old female. Note the activity is located at the base of the endosteal border of the hyperostosis. (D-F) Enhanced activity of the parietal area. Note the activity is not located in the endosteal part solely, but mainly at the base of the hyperostotic border.

In HCl the first abnormal findings are seen in the frontal bone (Figure 6.6). Generally, the endosteal abnormalities of the affected calvarial bones (frontal and parietal) are found at the base of the endosteal border of the hyperostotic region (Figure 6.5C-F and Figure 6.6).

Frontal bone area

The frontal bone area is a pathognomonic area in visual assessment. In young affected individuals (late first, early second decade), a typical enhancement pattern is observed (Figure 6.6). First subtle sclerotic changes of the skull are observed (CT). When abnormalities on CT are hardly visible, frontal endosteal activity is detected (Figure 6.6A). Hotspots are seen at sclerotic sites (CT) and diffusely enhanced areas are seen at hypodense hyperostotic areas (CT). Frontal bone uptake gradually becomes more explicit during the second decade and can become fulminant (Figure 6.6B). As soon as an endosteal border of bone apposition is visible, the abnormal activity is observed at the endosteal side of the diploë and not centrally in the endosteal border (Figure 6.6B-C). Later (>30 years), frontal bone activity gradually decreases and the process of hyperostosis extinguishes (Figure 6.6D-E).

Petrous bone area

A varying interindividual degree of pneumatization and increasing pneumatization throughout life make it difficult to precisely quantify bone metabolism in this region. Therefore visual assessment of the scans of HCl patients is important in that it shows a typical enhancement pattern. Affected adolescents and patients in their 20s have diffuse enhancement of the petrous bone apex in the region of the internal auditory canal (Figure 6.7A-B), representing active osteosclerosis and hyperostosis of the medial part of the petrous bone (the region around the internal auditory canal containing the facial and vestibulocochlear nerves). From the age of 30 onward the typical endosteal enhancement pattern can be recognised as earlier in the frontal area (Figure 6.7C-D). There is a diffuse hyperactive border at both the anterior and posterior side of the petrous bone, the latter vanishing with increasing age (Figure 6.7E). Throughout life, there is no disease involvement of the mastoid, middle and inner ear visible with ¹⁸F-fluoride PET, corresponding to the CT findings.

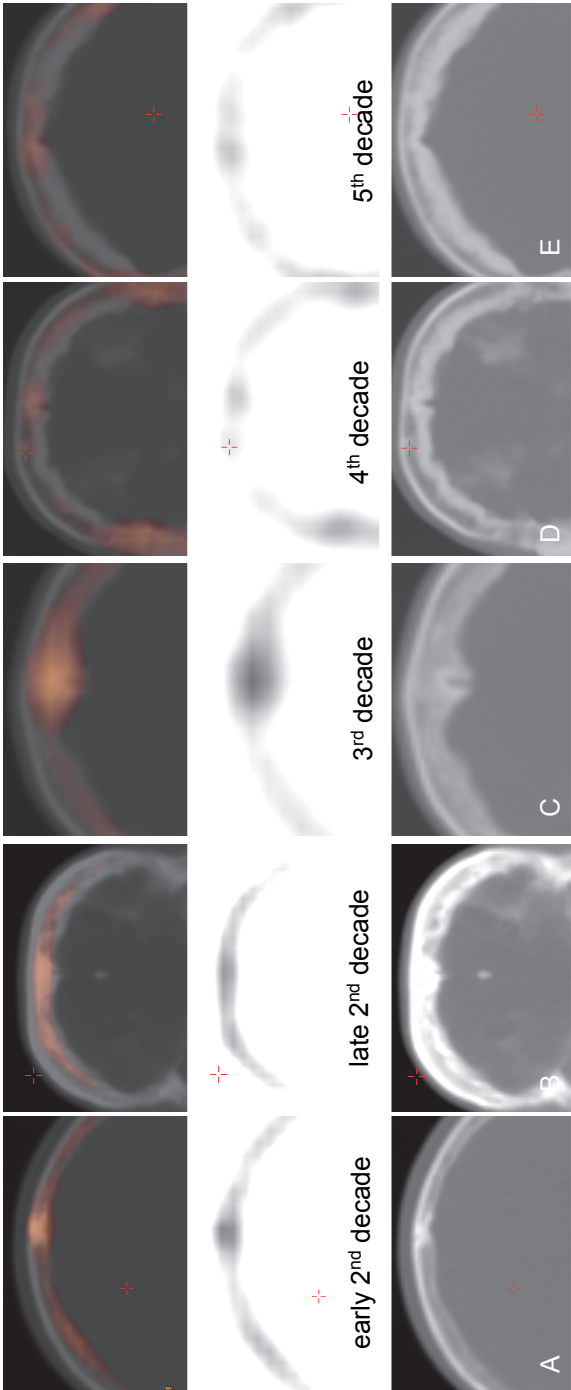


Figure 6.6 (A-E) Evolution of the disturbed bone metabolism throughout life in HCl patients, as observed in the frontal bone area. Note the outer cortex is not abnormal, however the endosteal border thickens during life.

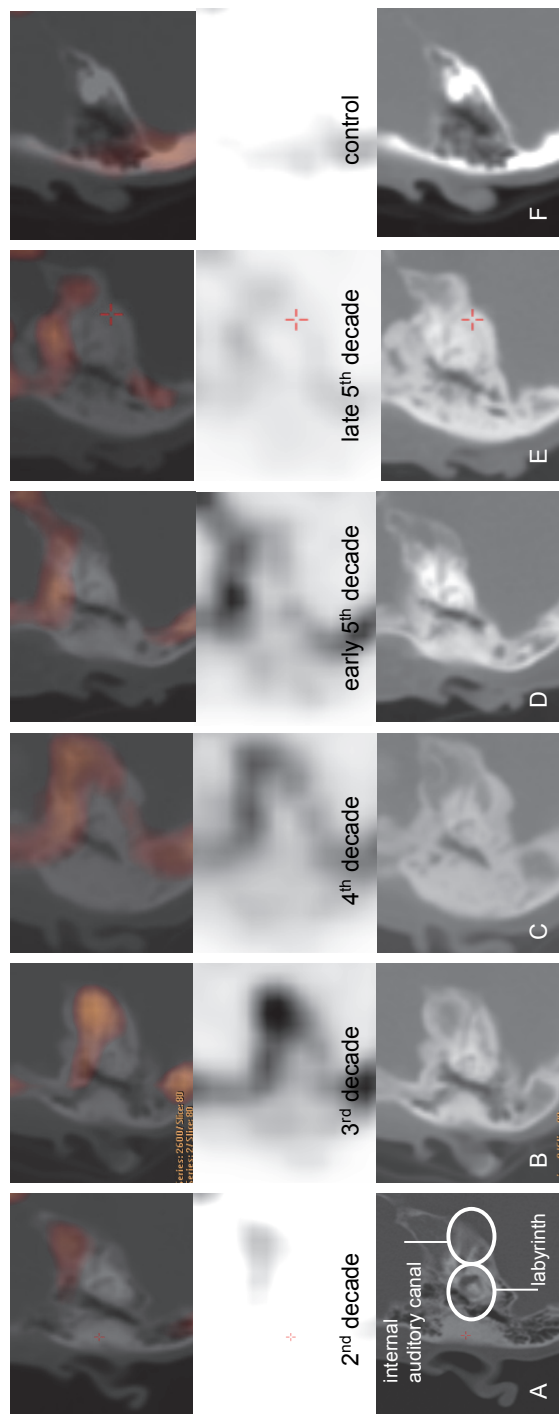


Figure 6.7 (A-F) Bone metabolic activity of the petrous bone throughout life (explanation in the text). There is important enhanced activity in the inner auditory canal region, corresponding with the facial and vestibulocochlear nerve impingement. Note the absence of enhancement in the control subject (age 29).

Sphenoid bone and temporal area

At the sites of fusion of the great wing of the sphenoid bone and the temporal and frontal bone (sphenopetrosal and sphenofrontal suture) there is enhancement in both affected as well as unaffected individuals. No typical pattern is visible in the abnormalities of the sphenoid bone area. Affected individuals have more pronounced activity at the surrounding endosteal part of the greater sphenoid wing. During life, an impressive endosteal border of additional bone forms at the level of the greater sphenoid wing and parietal bone, which remains more active than the sphenoid area in healthy individuals.

Data analysis

The results of the standard measurements for all groups together are shown in Table 6.1. Table 6.2 shows a breakdown of SUV parameters per group. The average SUV seems to be higher in group 1 for all locations except for the control site of the third cervical vertebra.

Table 6.1 Descriptive statistics for SUV_{mean} and SUV_{max} for all locations and all individuals (n=25).

Location	Mean SUV _{mean}	SD	Range	Mean SUV _{max}	SD	Range
Total uptake	1.56	0.48	0.83 – 2.62	-	-	-
Frontal bone	3.67	1.34	1.91 – 7.50	4.33	1.53	2.33 – 8.59
Clivus	5.32	1.52	2.49 – 8.75	6.01	1.77	2.87 – 9.85
Petrous bone (L&R)	4.09	1.35	1.86 – 8.27	4.86	1.55	2.09 – 9.41
Sphenoid bone (L&R)	5.50	1.74	2.80 – 11.82	6.21	2.01	3.34 – 13.77
3 rd cervical vertebra	7.83	2.34	4.09 – 15.42	8.79	2.65	4.50 – 17.76

SD = standard deviation, L&R = average of left and right

Table 6.2 SUV_{mean} and SUV_{max} for all bone locations for each of the different groups studied (n=25).

Location	SUV	Group			p-value	
		1 (n=9) HCI	2 (n=7) Family non-HCI	3 (n=9) Control	ANOVA	Kruskal- Wallis
Total uptake	Mean	1.74±0.55	1.49±0.21	1.44±0.55	0.412	0.427
Frontal bone	Mean	4.51±1.65	3.17±0.87	3.23±0.94	0.060	0.140
	Max	5.22±1.87	3.78±1.07	3.87±1.13	0.090	0.136
Clivus	Mean	6.17±1.38 [#]	5.70±1.36	4.18±1.12 [#]	0.010	0.016
	Max	7.00±1.61 [#]	6.43±1.70	4.70±1.22 [#]	0.011	0.023
Petrous bone	Max	4.47±1.56 [*]	3.93±1.31	3.82±0.96	0.534	0.542
	Mean	5.36±1.61	4.67±1.64	4.52±1.19	0.461	0.488
Sphenoid bone	Mean	6.58±1.62 ^{††}	5.66±1.21 [#]	4.30±0.93 ^{*#†}	0.004	0.007
	Max	7.48±1.88 ^{††}	6.36±1.29 [#]	4.82±0.97 ^{*#†}	0.003	0.006
3 rd cervical vertebra	Mean	7.28±1.71	8.18±2.22	8.09±3.05	0.701	0.859
	Max	8.17±1.93	9.12±2.36	9.16±3.54	0.693	0.873

^{*}Significantly different, $p \leq 0.01$ (Bonferroni T-test); [#], [†] Significantly different, $p \leq 0.01$ (Mann-Whitney)

The average SUV of the *complete skull* is not significantly higher for group 1 (SUV=1.74±0.55) when compared to groups 2 and 3 (1.49±0.21 and 1.44±0.55).

Uptake of ¹⁸F-fluoride in the *frontal region* (SUV_{mean}) is higher in the HCI group but no statistical significance is reached (ANOVA $p=0.06$, Kruskal-Wallis $p=0.14$). To investigate whether the outcomes were dependent on age, patients above and below the age of 40 were compared and on average the younger group had a 1.63 higher value, this difference being just barely statistically significant for the ANOVA ($p=0.049$) and not quite for the Kruskal-Wallis ($p=0.051$).

The group average SUV_{mean} in the *petrous bone region* is higher in HCI patients as compared to the other groups (group 1 4.47± 1.56 versus group 2 3.93±1.31 and group 3 3.82±0.96), but not statistically significant.

The *clivus and the sphenoid bone regions* have corresponding findings, although the sphenoid area is affected by HCI and the clivus does not show obvious hyperostosis. SUV_{mean} in the clivus area is 6.17±1.38 in group 1, 5.70±1.36 in group 2 and 4.18±1.12 in group 3. There is a statistical significance between group 1 and group 3 for both SUV_{mean} and SUV_{max} (t test $p=0.010$ and rank test $p=0.009$). SUV_{mean} in the sphenoid area is 6.58±1.62 in group 1, 5.66±1.21 in group 2 and 7.75±2.03 in group 3. SUV_{max} values show comparable results. In both areas age seems to influence the SUV values: group 2 values are positioned in between group 1 and 3, 1 being the highest (with youngest average age) and 3 the lowest (with highest average age). For the sphenoid area a statistically significant difference between group 2 and 3 is also found.

In Table 6.3 the SUV values of the hotspots in HCI-patients are displayed.

Table 6.3 Hot spots found in HCI-patients.

Location	SUV _{mean}	SUV _{max}
Frontal bone, skull base	6.49	7.25
	7.78	9.47
	8.60	9.85
	8.68	9.94
	9.24	10.69
	11.94	13.63
	12.91	15.61
Frontal bone, skullcap	4.77	6.45
	7.57	8.78
	7.82	9.09
	12.44	13.73
Occipital suture	7.40	8.82
	7.59	9.05
	8.03	9.24
	8.74 ^a	11.24 ^a
	9.09 ^a	11.71 ^a

The paired SUV_{mean} and SUV_{max} represent one hot spot in one patient. ^a Results from the same patient.

Discussion

Technical considerations concerning ^{18}F -fluoride PET/CT

To obtain reproducible outcome measurements several pharmacokinetic models have been described for ^{18}F -fluoride PET scans. Hawkins *et al.* developed a three-compartment model producing quantitative measurements for the net uptake of ^{18}F -fluoride into bone¹⁰. A rate constant (K) for this uptake can be calculated as a macroparameter using the individual rate constants described in the model obtained by nonlinear regression methods (NLR). This K_{NLR} provides a tool for measuring the bone turnover that correlates with biochemical data and bone histomorphometric analyses performed on biopsy samples^{14,15}. However it requires blood sampling and is therefore not widely used in clinical practice. Brenner *et al.* recognised this and compared the K_{NLR} to the more commonly used standardised uptake value (SUV) for semiquantitative metabolic bone measurements¹⁶. They found a strong positive linear correlation that was highly significant and reproducible. Thus, SUV is not only more practical and noninvasive but also equally reliable using ^{18}F -fluoride in PET imaging. Installé *et al.* confirmed this after comparing kinetic modelling, SUV and biochemical markers in monitoring the therapeutic response in Paget's disease of bone¹⁷. This study confirms the reproducibility of SUV in both unaffected as well as affected regions.

6

Standardised measurements of ^{18}F -fluoride uptake in HCI compared to healthy controls and non-affected family members

We analysed SUV_{max} and SUV_{mean} at different anatomic locations following a structured protocol. Both outcome measures give comparable results. Statistical power was limited by the small group sizes. Uptake in the third cervical vertebra served well as an internal control measurement. Statistically significant differences were found for various measurements of the sphenoid bone and clivus. With respect to the frontal measurement there is clearly a tendency, however missing power in the statistical analysis.

No significant differences were seen between the groups concerning the *total uptake of the skull*. A plausible explanation is the inclusion of normal bone tissue (the outer part of the skull) in group 1 within the ROIs, averaging the scores. Measuring total uptake was time-consuming and considering the results obtained it does not appear to be an efficient contribution.

Uptake in the *frontal bone* showed nearly statistically significant differences between the study groups. We did expect this difference because this part of the skull base and skullcap is unequivocally affected in patients and abnormalities develop especially in the first decades. The findings do encourage our hypothesis that in the frontal area the process of hyperostosis and osteosclerosis peaks in the first decades of life and settles

down thereafter. Typically there is no difference between group 2 and 3, regardless of the unequal age distribution.

The higher uptake of ¹⁸F-fluoride in the *petrous bone* of HCl-patients does correspond with our expectations, because the temporal bone is an affected region. Although the average uptake is higher in group 1 compared to group 2 and 3, this difference was not statistically significant. Different degrees of pneumatization are encountered and cannot be corrected for in this area. Another explanation, that becomes clear after visually studying the PET and CT scans, is the fact that the affected region of the petrous bone is confined to the endosteal border only.

Uptake in the *clivus and sphenoid region* are both significantly higher for the patients compared to the control group as well as compared to the family-non-HCl-group. The mean uptake values of unaffected family members are obviously between group 1 and 3 and this demands explanation. As opposed to other sites, these anatomical regions have in common that they are active growth centres (skull base sutures), explaining an increased local fluoride uptake in bone tissue representing osteoblastic activity^{18,19}. Increasing age is accompanied by a reduction of standard bone activity in these anatomical areas²⁰.

Value of visual assessment in HCl

¹⁸F-fluoride PET is a very sensitive imaging technique. Hot spots are found long after surgical interventions (mastoidectomy, optic nerve decompression) and after facial trauma (nasal and cheek bones). Also, larger regions with a diffusely increased uptake are not necessarily pathological. Craniofacial sutures and growth centers (such as the clivus) have diffusely enhanced ¹⁸F-fluoride uptake, congruent to the objective measurements.

PET activity in the petrous bone region is confirmed by clinical findings. Facial nerve palsy and vestibulocochlear nerve impairment generally occur in the first 30 years of life due to impingement of the nerve at the level of the internal auditory canal, where increased PET activity is then observed. Along with the lifetime progression of hyperostosis, one would expect progression to complete facial paralysis and deafness. Typically, the PET activity in this region surrounding the internal auditory canal decreases, explaining why the clinical symptomatology remains stable (Figure 6.7).

Clinical application of ¹⁸F-fluoride PET/CT for HCl and bone metabolic disorders in general

In studies using ¹⁸F-fluoride there is limited experience with SUV in spite of the advantages and proven reliability^{16,17}. Uchida *et al.* demonstrated differences in SUVs in the lumbar spine after alendronate treatment in osteoporosis patients²¹. Reference SUV scores of different areas of normal bone with this tracer are scarcely described in

literature. No other studies were found with a detailed description of average uptake values of unaffected bone in different anatomical sites.

CT scanning will remain the gold standard for the diagnosis of HCl because of its high resolution. However, there is a need to quantify the disease activity rather than to perform sequential CT scans. This study confirms that ^{18}F -fluoride PET/CT is a very sensitive imaging technique in determining disease activity, showing differences in small population sizes. The indolent character of this metabolic disorder raises an important limitation: there is a narrow window between normal and pathologic metabolic activity. Therefore SUV measurements should always be accompanied with the visual interpretation of changing bone activity patterns over time in different regions.

Age is the most important covariate to take into account in regions with a high bone turnover (i.e. sphenoid and clivus area) as osteoblastic activity diminishes with increasing age resulting in a lower uptake of ^{18}F -fluoride²⁰. In this study we had difficulties finding young individuals to serve as appropriate control subjects. This caused an unequal age distribution in the different groups and was therefore potentially one of the most serious drawbacks of this study. To overcome this, group 2 (non-affected family members) with a similar age distribution as group 1 served as a secondary control group and showed similar results as group 3.

This study uses the semiquantitative SUV ratio for the first time in a case-control study. The use of a consistent internal control site is important as an internal validation check of correct SUV processing. ^{18}F -fluoride PET/CT, analysed by SUV, appears to be reliable since we found differences supporting our hypotheses. If the aforementioned limitations are taken into account, the combination of SUV measurements and visual interpretation can be of important value and might bring ^{18}F -fluoride PET/CT closer to being a diagnostic test for metabolic bone diseases.

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Chapter 7

Bone turnover markers and histology of hyperostosis cranialis interna

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Submitted

Abstract

In hyperostosis cranialis interna, hyperostotic and sclerotic changes take place at the level of the calvaria and the skull base. It is not yet known whether this results from increased bone formation, decreased bone resorption or increased bone turnover. Biochemical examination of serum was performed on patients and unaffected family members to search for abnormalities in general and specific bone related serum markers. No significant differences were found between both groups in the levels of routine serum markers. Serum C-terminal propeptide of type I collagen (PINP), a marker of bone formation was found to be relatively lower in patients than the unaffected individuals. The value of this contradictory finding in this very slowly progressing and highly localised bone dysplasia remains unclear until the exact pathogenesis of the disorder is discovered. Furthermore histologic images are provided of bone biopsies obtained during a craniotomy of a patient with HCI.

Introduction

Hyperostosis cranialis interna (HCI) is a rare autosomal dominant sclerosing bone dysplasia with progressive hyperostosis and osteosclerosis of the calvaria and the skull base. Its clinical course and radiological findings have recently been described^{1,2}. Patients mainly suffer cranial nerve dysfunction due to bony narrowing of the affected neuroforamina, especially facial nerve palsy, sensorineural hearing loss, anosmia and trigeminal neuropathy. The pathophysiologic mechanism is still unknown. The inner table of the calvaria thickens and becomes sclerotic, as well as the endosteal cortical bone layer of the skull base, beginning usually before the age of 10 (Figure 7.1).



Figure 7.1 Axial computed tomography of a 23-year-old affected woman at the level of the orbits, the greater sphenoid wings, the temporal bones and the occipital bone. Note the remarkably thickened and relatively hypodense endosteal cortices and the sclerotic olfactory area. The marrow space (diploë) is not obliterated and the outer table is spared.

To assess local bone metabolic activity ¹⁸F-fluoride PET/CT has shown to be useful, generally displaying increased ¹⁸F-Fluoride in affected areas in patients with active disease, suggesting increased bone metabolism plays a role in the pathophysiological mechanism³. In this group of patients with HCI biochemical bone markers have been determined.

Even with present sensitive bone turnover markers it is a challenge – if possible at all – to detect altered bone metabolism with clinical chemical markers in patients with highly localised disordered metabolism such as in HCI. Biochemical markers have been proven to be reliable in other rare – systemic – bone dysplasias to assess disease

activity or therapeutic response: Paget's disease⁴, osteogenesis imperfecta^{5,6}, Van Buchem disease⁷, Camurati-Engelmann disease⁸ and McCune-Albright syndrome⁹.

In patients with HCl the abnormal progression of cranial bone formation and osteosclerosis is most pronounced at the end of the first and during the second and third decades of life, later the process of hyperostosis gradually slows down. The bone density of the hyperostotic endosteal bone is radiologically less dense than the usual cortical bone (>1250 Hounsfield Units on computed tomography and is called porous cortical bone (850-1250 HU) according to the classification proposed by Misch *et al.*, used in the oral implantology¹⁰. An extra challenge in assessing (abnormal levels of) bone turnover markers in HCl rises realising that average bone mass in healthy individuals has a variable course: an increase until mid-20s (similar to the period of most active disease in HCl patients). After that there is stable bone mass until approximately 40, after which it decreases, more rapidly in postmenopausal women. The aim of this study is to evaluate whether bone turnover markers in patients affected with HCl are altered compared to healthy individuals.

Materials and methods

Blood was drawn from 9 affected individuals (mean age 32 years, range 9-68 years) and 12 unaffected family members (mean age 19 years, range 3-42 years) (Figure 7.2). Given the results of genetic data (linkage analysis), some of the children are excluded with the diagnosis HCl although they have not yet reached the age at which radiological abnormalities become apparent (again Figure 7.2.)¹¹. The young affected individuals do have radiological abnormalities.

The following clinical chemical investigations were performed: total serum calcium level, ionised serum calcium level, albumin, parathyroid hormone (PTH) and 25-hydroxy vitamin D. Reference values for serum levels of 25-hydroxy vitamin D are subject to discussion in international literature^{12,13}. A minimal reference value of 50 nmol/l was used. This value was chosen, since above this concentration there is no relation anymore between vitamin D concentration and bone metabolism. However, it is known that for non-skeletal functions of vitamin D, much higher vitamin D concentrations are necessary¹⁴.

Serum C-terminal propeptide of type I collagen (PINP) was determined to measure bone formation. To measure bone resorption cross-linked telopeptide of type I collagen (ICTP) was determined in serum (the advantage of ICTP compared to other bone resorption markers such as pyridinoline and deoxypyridinoline is that no urine sampling is needed). Both were assessed by radioimmunoassay (Orion Diagnostica, Espoo, Finland). Paediatric PINP reference values were adopted from Crofton *et al.*¹⁵. For ICTP those provided by the manufacturer of the immunoassay were used.

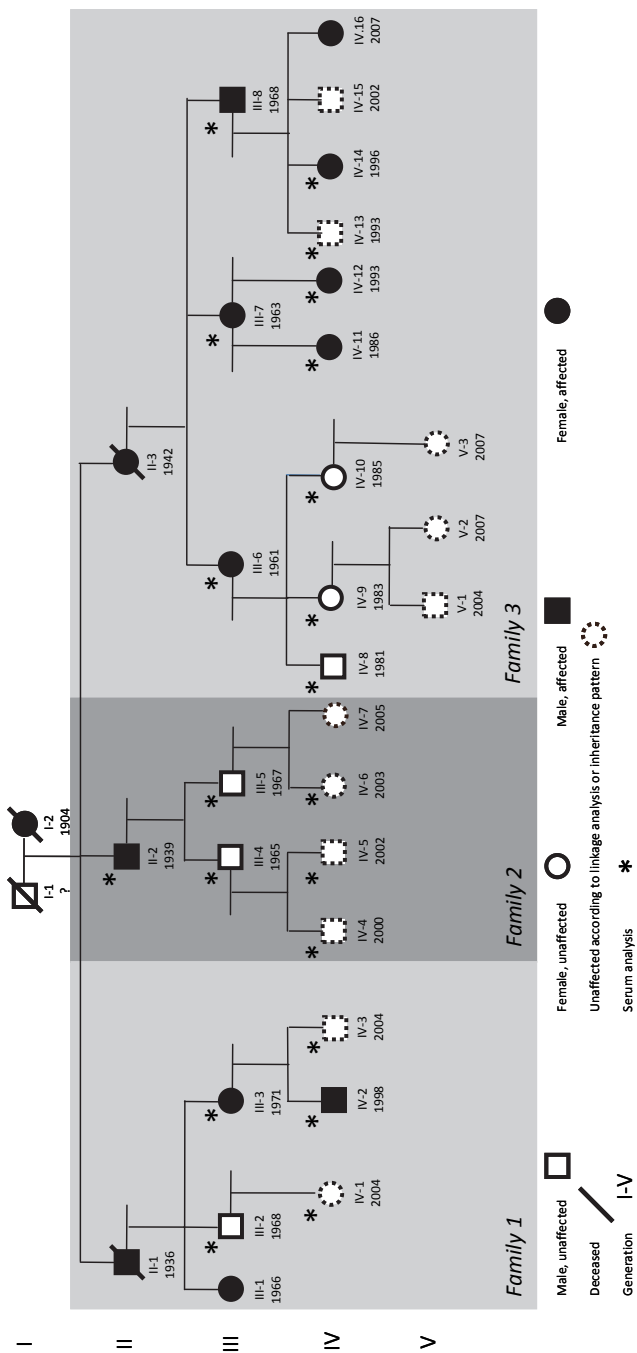


Figure 7.2 Pedigree of the affected family.

Bone biopsies were obtained during a craniotomy and embedded in paraffin in the Maastricht University Medical Center. The decalcification and sectioning of the tissue was performed in the Leiden University Medical Centre, a department specialised in handling and diagnosing bone specimens of rare disorders and bone tumours. Haematoxylin and eosin stainings were made in Maastricht again.

Results

Serum markers

All total serum calcium levels, ionised calcium levels, albumin levels and PTH levels were within the age-adjusted reference values in both affected individuals and the unaffected family members (Table 7.1). One patient had a low vitamin D level (III-6). ICTP and PINP levels are plotted with age-adjusted reference values in Figures 7.3 and 7.4.

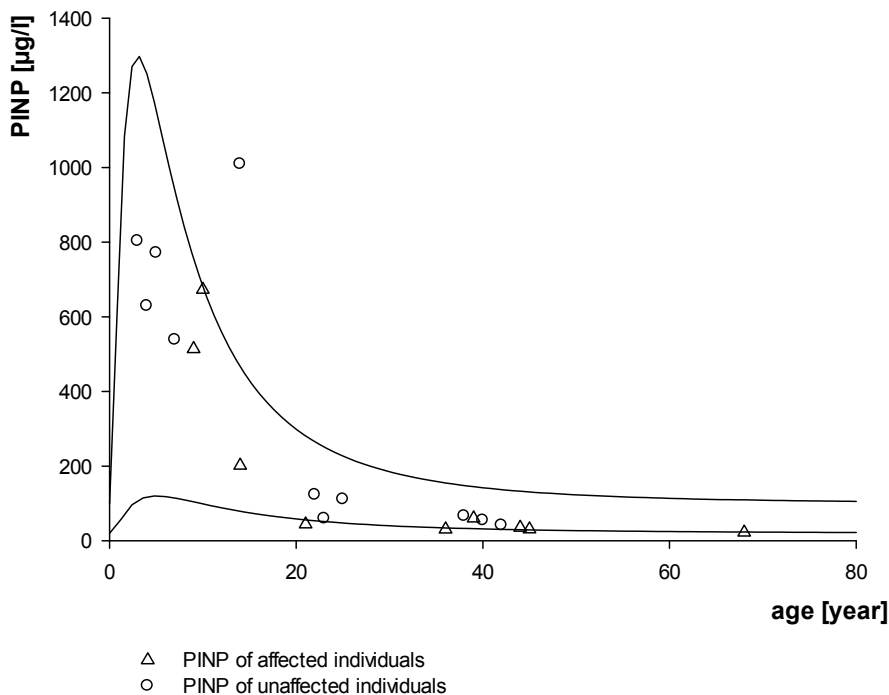


Figure 7.3 PINP values with references for both groups. The lines represent an approximation of the normal values of PINP concentrations with a four parameter log normal distribution (normal values cannot be calculated since the number of observations is too small).

Table 7.1 Bone turnover markers in patients and unaffected family members.

Nr	Sex	Age	CalciumTot (2.10–2.55 mmol/l)	Calciumlon (1.10–1.30 mmol/l)	Albumine (32.0–47.0 g/l)	PTH (1.3–6.8 pmol/l)	VitD25 (>50 nmol/l)	PINP (µg/l)	PINP ref [*] (µg/l)	ICTP (µg/l)	ICTP ref [*] (µg/l)
Affected individuals											
IV-2	M	9	2.38	1.22	44.7	5.0	63	514	184-1024	9.8	7.0-16.0
IV-14	F	10	2.50	1.30	45.3	2.3	63	<u>673</u>	237-635	11.6	8.0-15.0
IV-12	F	14	2.34	1.22	38.8	3.5	106	201.3	116-490	<u>6.6</u>	2.1-5.6
IV-11	F	21	2.34	1.23	39.9	2.8	86	44.2	19-83	3.1	2.1-5.6
III-3	F	36	2.27	1.23	38.3	3.9	93	30.7	19-83	2.1	2.1-5.6
III-8	M	39	2.34	1.25	40.2	2.3	62	60.4	22-87	2.5	2.1-5.0
III-7	F	44	2.31	1.21	36.8	2.8	85	35.2	19-83	2.4	2.1-5.6
III-6	F	45	2.14	1.19	33.0	2.5	<u>42</u>	31.2	19-83	2.8	2.1-5.6
II-2	M	68	2.26	1.22	37.6	6.5	81	22.4	22-87	3.7	2.1-5.0
Unaffected family members											
IV-3	M	3	2.38	1.29	43.8	6.4	67	missing	184-1024	14.8	7.0-16.0
IV-1	F	3	2.47	1.27	43.8	1.2	73	803	184-1024	12.3	7.0-16.0
IV-6	F	4	2.55	1.35	44.9	4.8	96	629	184-1024	11.6	7.0-16.0
IV-5	M	5	2.44	1.23	45.5	4.8	88	771	184-1024	14.0	7.0-16.0
IV-4	M	7	2.44	1.23	47.5	3.0	84	538	184-1024	10.8	7.0-16.0
IV-13	M	14	2.38	1.25	39.3	2.4	59	1009	202-1212	15.1	10.0-23.0
IV-10	F	22	2.26	1.22	37.1	1.7	72	<u>122.5</u>	19-83	<u>13.5</u>	2.1-5.6
IV-9	F	23	2.32	1.27	42.9	2.9	75	59	19-83	4.8	2.1-5.6
IV-8	M	25	2.43	1.20	47.7	1.3	72	<u>110.6</u>	22-87	3.5	2.1-5.0
III-3	M	38	2.42	1.22	48.3	2.6	102	65.8	19-83	2.5	2.1-5.6
III-5	M	40	2.22	1.20	42.0	4.8	72	54.3	22-87	3.7	2.1-5.0
III-4	M	42	2.33	1.23	42.5	5.6	62	40.9	22-87	3.5	2.1-5.0

* PINP ref & ICTP ref = reference values adjusted for age; underscored and bold: outside reference range

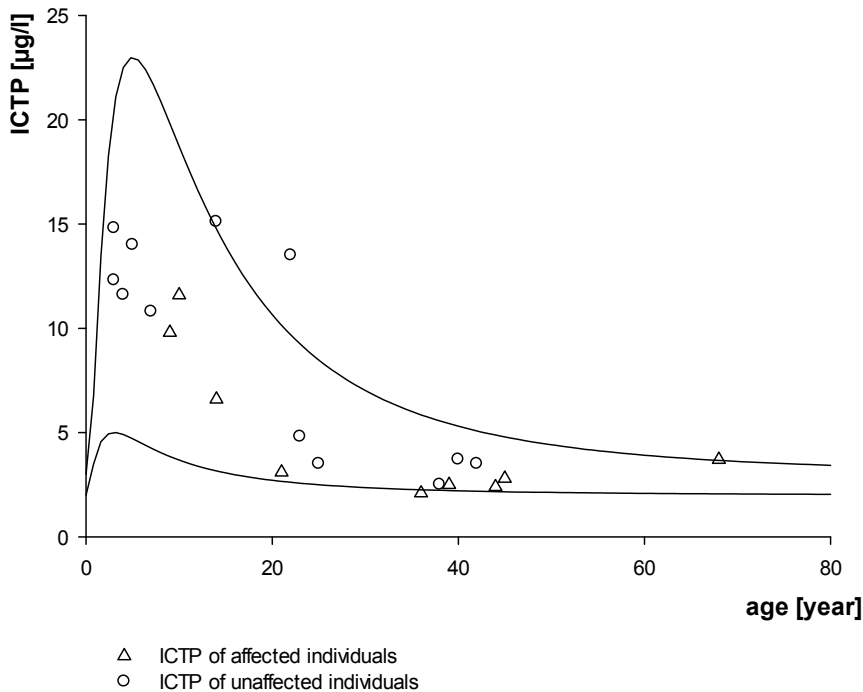


Figure 7.4 ICTP values with references for both groups. The lines represent an approximation of the normal values of ICTP concentrations with a four parameter log normal distribution (normal values cannot be calculated since the number of observations is too small).

7

Because the reference values of ICTP and PINP are greatly subject to age and gender and have a large spread, the outcome values (x) of both patients and unaffected family members were compared to the mean reference value and its standard deviation (SD). Reference values for the kit used are set as the mean outcome (age-adjusted) $\pm$ 2SD. For each individual an age-adjusted Z-score was calculated (Table 7.2), representing the relative deviation off the average expressed in standard deviation:

$$Z = \frac{x - x_{\text{meanreference of age group}}}{SD}$$

We performed non-parametric rank tests (Mann-Whitney test) to assess whether there was a difference in Z-scores between affected and unaffected individuals. It appeared that unaffected individuals had significantly more often higher PINP Z-scores than affected individuals ($p=0.009$, Figure 7.5), pointing towards relatively higher bone formation serum levels for unaffected individuals. An important difference between both groups was the presence of 5 children aged 7 or less in the group of unaffected

family members. When subjects <18 years were censored, the difference between the Z-scores was statistically significant ($p=0.016$). No differences were found between the Z-scores of ICTP in both groups.

Table 7.2 PINP and ICTP values with their Z-scores.

Nr	Sex	Age	PINP ($\mu\text{g/l}$)	<i>PINP ref</i> [†] ($\mu\text{g/l}$)	Z-value PINP	ICTP ($\mu\text{g/l}$)	<i>ICTP ref</i> [†] ($\mu\text{g/l}$)	Z-value ZICTP
Affected individuals								
IV-2	M	9	514	184-1024	-0.43	9.8	7.0-16.0	-0.76
IV-14	F	10	<u>673</u>	237-635	2.38	11.6	8.0-15.0	0.06
IV-12	F	14	201.3	116-490	-1.09	<u>6.6</u>	2.1-5.6	3.14
IV-11	F	21	44.2	19-83	-0.43	3.1	2.1-5.6	-0.86
III-3	F	36	30.7	19-83	-1.27	2.1	2.1-5.6	-2.00
III-8	M	39	60.4	22-87	0.36	2.5	2.1-5.0	-1.45
III-7	F	44	35.2	19-83	-0.99	2.4	2.1-5.6	-1.66
III-6	F	45	31.2	19-83	-1.24	2.8	2.1-5.6	-1.2
II-2	M	68	22.4	22-87	-1.98	3.7	2.1-5.0	0.21
Unaffected family members								
IV-3	M	3	missing	184-1024	missing	14.8	7.0-16.0	0.36
IV-1	F	3	803	184-1024	0.95	12.3	7.0-16.0	0.04
IV-6	F	4	629	184-1024	0.12	11.6	7.0-16.0	1.47
IV-5	M	5	771	184-1024	0.80	14.0	7.0-16.0	1.11
IV-4	M	7	538	184-1024	-0.31	10.8	7.0-16.0	-0.31
IV-13	M	14	1009	202-1212	1.20	15.1	10.0-23.0	-0.43
IV-10	F	22	<u>122.5</u>	19-83	4.47	<u>13.5</u>	2.1-5.6	11.03
IV-9	F	23	59	19-83	0.5	4.8	2.1-5.6	1.09
IV-8	M	25	<u>110.6</u>	22-87	3.45	3.5	2.1-5.0	-0.07
III-3	M	38	65.8	19-83	0.93	2.5	2.1-5.0	-1.54
III-5	M	40	54.3	22-87	-0.01	3.7	2.1-5.0	0.21
III-4	M	42	40.9	22-87	-0.84	3.5	2.1-5.0	-0.07

[†] PINP ref & ICTP ref = reference values adjusted for age

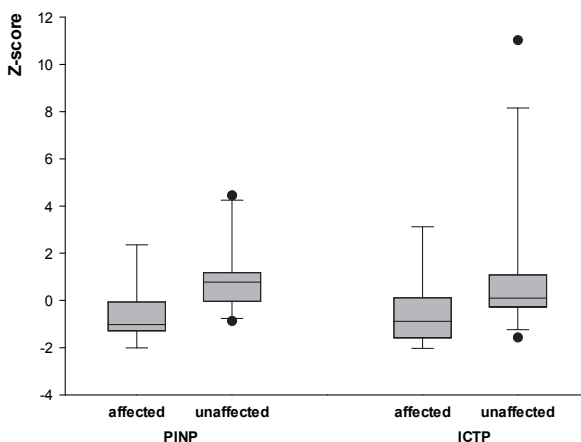


Figure 7.5 Box plots of affected and unaffected individuals for PINP and ICTP: the boxes correspond to the 25th and the 75th percentiles; the error bars show the 5th and 95th percentiles; the lines in the boxes correspond to the median. Outliers are indicated with a black dot.

Histology

Figures 7.6-9 display the light micrographs of the sectioned biopsies. These are haematoxylin and eosin stainings showing irregular trabecular bone without evident osteoblastic lining. No obvious osteoclastic activity of note is present either. The bone trabeculae have irregular basophilic kit lines with irregular deposition of woven bone. Please note the presence of prominent bone tunnelling. The scale bar in each figure can be used as a reference.

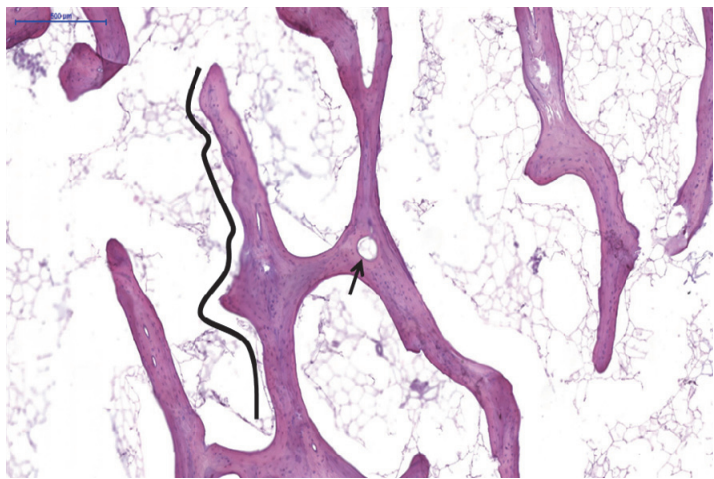


Figure 7.6 Haematoxylin and eosin staining of trabecular bone surrounded by fat. The scale bar in the upper left corner corresponds with 500 μm . The arrow indicates the prominent bone tunnelling. The trabecular bone is irregularly fomed (black curved line).

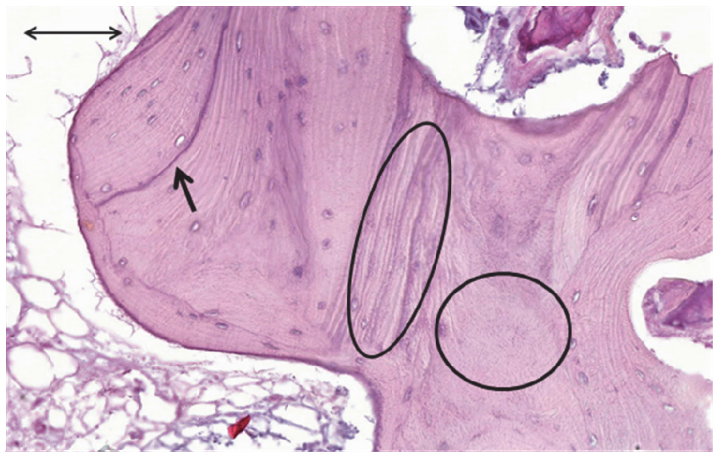


Figure 7.7. The scale bar in the upper left corner corresponds with 100 μm . The only present bone cells are

osteocytes. Some areas are organised as lamellar bone (oval), but there are also areas with woven bone (circle). The arrow points at a basophilic kit line.

Conclusion and discussion

General bone-related serum markers do not differ in patients with HCI. This is not surprising, taking into consideration that the skull accounts for only approximately 10% of the total bone mass and that the process of hyperostosis in HCI proceeds only very slowly. Any supposedly statistically significant difference, such as the Z-values of PINP being higher in the unaffected group, is therefore highly questionable, especially because the values of this sensitive bone formation marker are subject to many non-HCI-related factors. Moreover, there is a large (physiological) spreading of concentrations. Intuitively one would expect the bone formation markers to be higher in affected patients. If the observed difference with respect to PINP is disease-related, this would point to a disturbed balance of the bone metabolism. To conclude that there is a disbalance between formation and resorption of bone (in favour of formation), the ICTP values (bone resorption) would have to be relatively more decreased than the PINP values (bone formation) in affected individuals. However, ICTP does not show any tendency at all towards lower values to obtain this net difference. Consequently, the observed significant difference (relatively lower bone formation parameter PINP) is remarkable, but at this moment we do not know the etiology. Other markers of bone resorption should be looked for to discover the one that counteracts the lowered PINP in patients. Unfortunately however, patients' samples of our study population are exhausted.

The histologic part of this study reveals that the affected bone that is found in the biopsy consists of trabecular bone. Hardly any active bone cells were seen in the specimens, only osteocytes. It is peculiar to find woven bone at this location instead of lamellar bone, suggesting a local disturbance in the bone metabolism. Woven bone is usually found after a fracture or infection and in some bone tumours but not in slowly growing and remodelling bone tissue.

Ten to 20% of osteoblasts differentiate into osteocytes¹⁶. Osteocytes are supposed to produce an inhibitory signal to osteoblasts, which are involved in bone formation and consequently, they are important regulators of bone mass¹⁷. But the absence of osteoblasts and osteoclasts might be an indication of disturbance of this (local) regulation. It is conceivable, that the absence of osteoblasts and osteoclasts results in lowered PINP and ICTP. It is clear that a lot of research has to be done to unravel the very subtle mechanism of bone formation and degradation, especially in HCI, this disease being so rare.

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Part III

Genetics of hyperostosis cranialis interna

Chapter 8

Localisation of the gene for hyperostosis cranialis interna to chromosome 8p21 with analysis of three candidate genes

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Abstract

Hyperostosis Cranialis Interna (HCI) is a rare autosomal dominant disorder characterised by intracranial hyperostosis and osteosclerosis which is confined to the skull, especially the calvaria and the skull base. The rest of the skeleton is not affected. Progressive bone overgrowth causes nerve entrapment leading to facial nerve palsy, disturbance of the sense of smell, hearing and vision impairments, impairment of facial sensibility and disturbance of balance due to vestibular dysfunction. The treatment is symptomatic. Until today the disease has been described in only three related Dutch families with common progenitors and which consist of 32 individuals over five generations. HCI was observed in 13 family members over four generations. Patients are mildly to severely affected. Besides HCI, several bone dysplasias with hyperostosis and sclerosis of the craniofacial bones are known. Examples are Van Buchem disease, sclerosteosis, craniometaphyseal dysplasia and Camurati-Engelmann disease. However, in these cases the long bones are affected as well.

Linkage analysis in a family with HCI resulted in the localisation of the disease-causing gene to a region on chromosome 8p21 delineated by the markers D8S282 and D8S382. Interesting candidate genes in this region were *BMP1*, *LOXL2* and *ADAM28*. Sequence analysis of these genes did not reveal any putative mutations. This suggests that a gene not previously involved in a sclerosing bone dysplasia is responsible for the abnormal growth in the skull of these patients.

Introduction

Sclerosing bone disorders are a group of skeletal abnormalities of varying severity with a wide range of clinical, radiologic and genetic features. These disorders are caused by decreased bone resorption, increased bone formation or increased bone turnover¹. Identifying genes responsible for these conditions could give new insights in bone metabolism and could lead to new targets for the treatment of osteoporosis. In most conditions, the whole skeleton is affected.

Hyperostosis cranialis interna (HCl) is a rare autosomal dominant disorder characterised by endosteal hyperostosis and osteosclerosis of the calvaria and the skull base. The remainder of the skeleton is unaffected. The disease was first described in 1990 by Manni *et al.*². The facial appearance and the shape of the head are normal. Small mandibular exostoses develop intraorally later in life, one on each side. The first symptoms can occur in adulthood or even late in the first decade; however, the first radiological abnormalities are often seen in the first decade^{2,3}. CT scans show bony overgrowth of the temporal bone and narrowing of the internal auditory canals, the optic canals and the orbital fissures (Figures 8.1-3). This leads to entrapment and dysfunction of cranial nerves I, II, V, VII and VIII, causing recurrent facial nerve palsy, disturbance of the sense of smell, anosmia, hearing and vision impairments and disturbance of balance due to vestibular dysfunction³. In addition, increased ocular and intracranial pressure can occur. The progressive functional impairment of facial and vestibulocochlear nerve function might be due to direct effect of pressure on the nerve fibers or impairment of the blood supply^{4,5}. A slow progression of the disease can be seen until the age of 40. After the fourth decade, radiological progression is minimal and progressive cranial nerve dysfunction is uncommon in most^{3,6}. However, untimely death may occur in severely affected cases, due to decreased intracranial volume³.

The biopsy specimen of the iliac crest was normal². Several markers of bone turnover were tested and calcium, albumin, parathyroid hormone and 1,25-dihydroxyvitamin D₃ showed no abnormal values.

To date, no causal treatment for HCl is available. Symptomatic treatment may consist of hearing aids in case of moderate sensorineural hearing loss. Decompressive surgery can be performed to treat facial and vestibulocochlear nerve compression^{3,5}. Facial nerve decompression via middle cranial fossa approach has been successfully performed⁵. In case of threatened vision due to optical canal narrowing, optic nerve decompression can be performed.

Numerous bone dysplasias with hyperostosis of the calvaria and the skull base exist. Van Buchem disease⁷, Camurati-Engelmann disease⁸, and sclerosteosis⁹ are examples of diseases with increased bone density with involvement of the skull. However, in these disorders, the long bones are affected as well, whereas in HCl only the skull is affected. In order to localise the gene for HCl, we performed a genetic linkage study in a Dutch family with HCl.

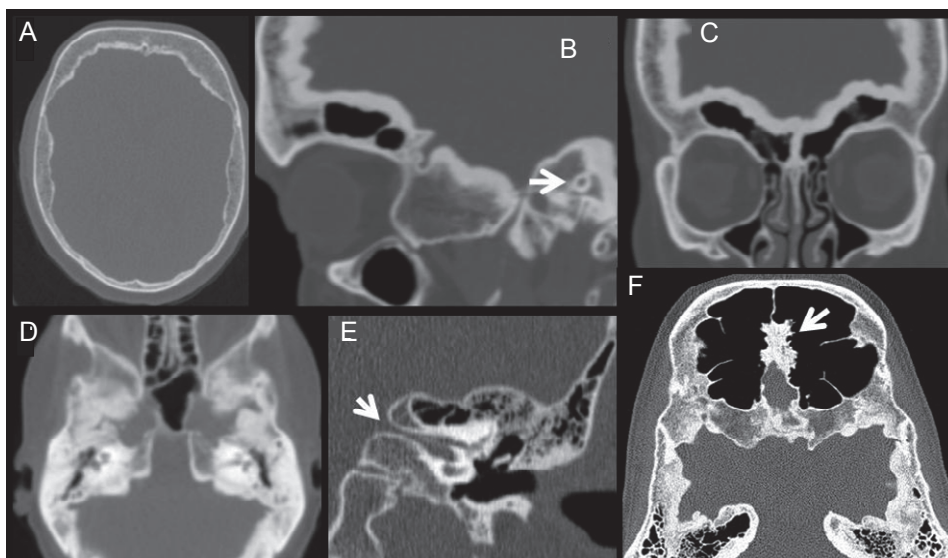


Figure 8.1 CT imaging. (A) Axial image of individual III.8. Note that the frontal and parietal bones are affected. Note the diploë is not obliterated. (B) and (C): Sagittal and coronal reconstructions of III.3. Evident endosteal apposition of bone at the base of skull, whereas the facial bones are unaffected. Arrow: narrowed internal auditory canal. (D) Axial image of III.6. Typically the region of the greater wing of the sphenoid bone and the squama temporalis are most severely affected. (E) Narrowing of the internal auditory canal due to endosteal apposition (arrow) in IV.14 (coronal reconstruction). (F) Axial image of the anterior and middle fossa of III.1. Arrow: osteosclerosis of the olfactory region. From: "Phenotypic manifestations and management of hyperostosis cranialis interna, a hereditary bone dysplasia affecting the calvaria and the skull base". *Am J Med Genet A*, 152A, 2010, p547-555 © Wiley-Liss, Inc. This material is reproduced with permission from John Wiley & Sons, Inc.

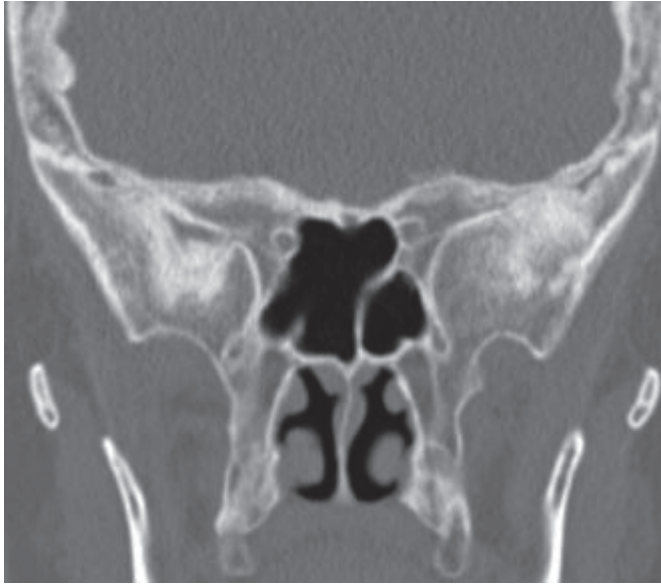


Figure 8.2 41-year-old woman. Coronal CT image at the level of the sphenoid sinus. There is endosteal hyperostosis of the greater and lesser wings of the sphenoid bones and of the parietal bones.

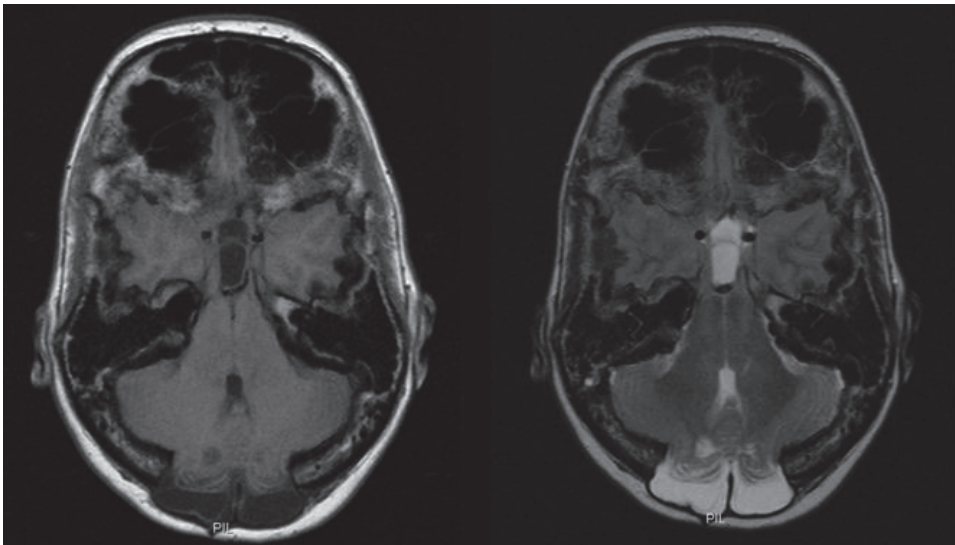


Figure 8.3 Patient (female, 38) with longstanding complaints of headache. A foramen magnum decompression was performed because of Chiari I malformation. Axial T1 (left) and T2 (right) images without contrast. Note the indentation of the temporal lobes.

Families and methods

Family

To date, the disease has only been described in three related Dutch families. They have common progenitors and consist of 31 individuals in five generations^{2,3}. HCl was observed in 13 family members over four generations (Figure 8.4). The disease is segregating in an autosomal dominant mode of inheritance and so far no evidence for incomplete penetrance is available.

The diagnosis of HCl is based on radiological and physiological examinations and confirmed by computed tomography. An individual without radiographic abnormalities at the age of 18 is considered unaffected as the median age of onset is 14³. Eleven individuals without abnormalities have not yet reached this age (Figure 8.4). All persons gave their informed consent prior to their inclusion to the study.

Genotyping and linkage analysis

Peripheral blood was collected from 24 family members and five nonrelated partners. Genomic DNA was isolated from these blood samples using standard procedures.

A whole-genome scan was performed on 11 patients (II.1-3, III.1, III.3, III.6-8, IV.11-12, IV.14), 6 unaffected family members (II.2, III.4-5, IV.8-10) and 5 unrelated partners (II.4-6, III.9-10). The Weber Lab Screening Set 16 was used. This set contains 404 fluorescently labelled, highly polymorphic microsatellite markers, covering the entire genome, with an average spacing of 9 cM. The markers are mainly tri- or tetranucleotides and have an average heterozygosity of 72%. The markers were analysed by use of an automated DNA-sequencing apparatus (Applied Biosystems, Foster City, CA, USA). Extra markers for regions of interest were chosen from the Marshfield genetic map¹⁰. These markers were analysed by a GoTaq DNA polymerase-mediated PCR (Promega, Madison, WI, USA), with fluorescently labelled primers¹¹. Fragment analysis of amplified products was performed using an ABI PRISM® 3130 XL Genetic Analyzer (Applied Biosystems). Allele identification was done with Gene mapper v3.7 software (Applied Biosystems).

Linkage analysis was performed using the EasyLinkage v4.01 program^{12,13}. Multipoint LOD scores were calculated with SimWalk v2.91 under the assumption that HCl is an autosomal dominant disease with a disease frequency of 1/10,000. For all calculations, a penetrance of 100% and a phenocopy rate of 0% were used.

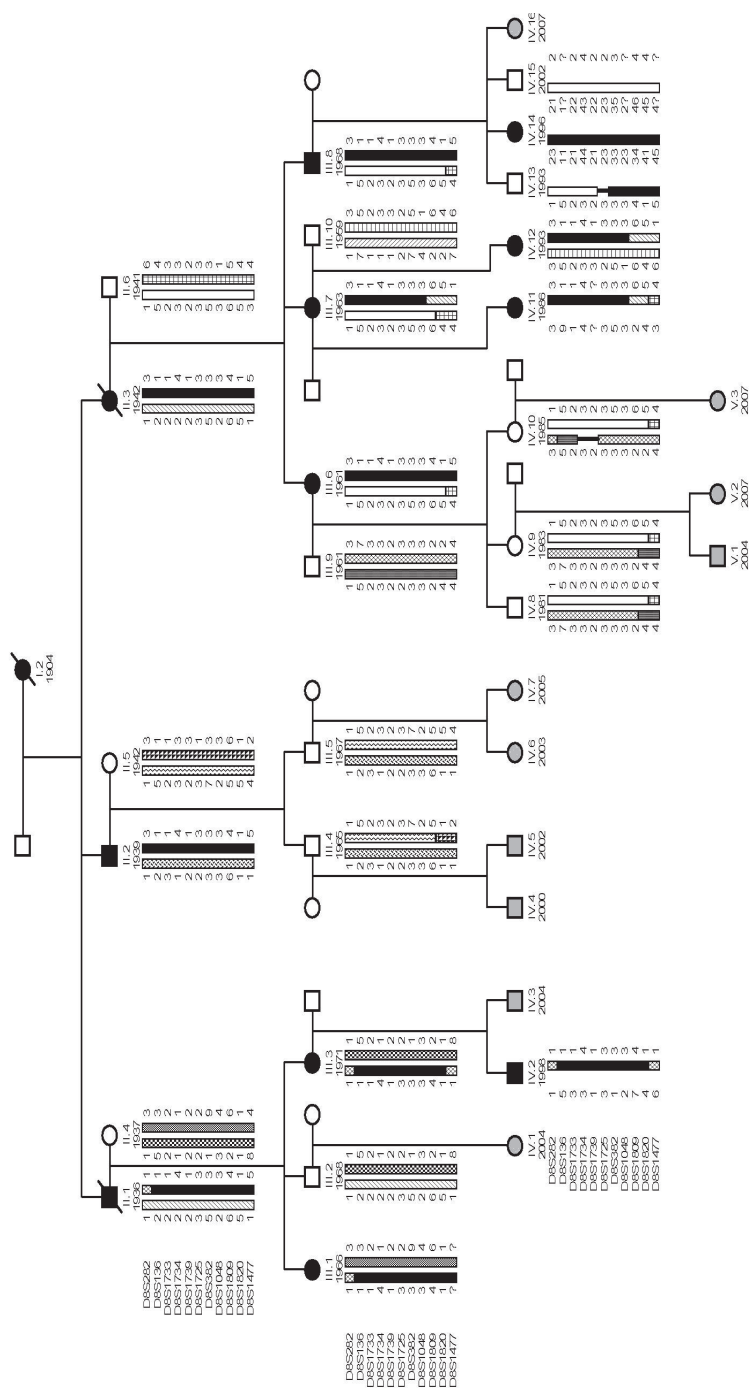


Figure 8.4 Pedigree of family with HCl including 13 patients over 4 generations. Black symbols represent affected individuals. Grey symbols represent individuals that are too young to be excluded. White symbols indicate unaffected individuals. The region above marker D8S282 and below D8S382 is excluded based on recombination events.

Sequence analysis of candidate genes

Sequence analysis was performed on DNA of one affected individual (IV.14, Figure 8.4), one healthy family member (IV.9, Figure 8.4) and an unrelated control sample. Genes were amplified by GoTaq DNA polymerase-mediated PCR. The PCR amplifications were carried out with a set of primers covering the exons and intron-exon boundaries. Primers for each exon were selected in an intronic sequence at approximately 100 bp away from the intron-exon boundaries.

Sequencing reactions were performed using the ABI BigDye Terminator v1.1 Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Foster City, California, USA). Purification with the BigDye Terminator Purification Kit (Applied Biosystems) was carried out to remove unincorporated BigDye terminators, after which fragments were analysed on an ABI 3130 Genetic Analyzer (Applied Biosystems).

Results

Linkage analysis

After testing 404 polymorphic microsatellite markers which covered the entire genome, multipoint LOD scores were calculated with EasyLinkage v4.01. Ninety-six percent of the chromosomal regions were immediately excluded based on multipoint LOD scores below -2, while only one region showed LOD scores above +3.

Genes known to cause sclerosing bone dysplasias with involvement of the skull, like *LRP4*, *LRP5*, *SOST* and *TGFB1* could also be excluded as disease causing genes based on LOD scores below -2.

Multipoint LOD scores showed positive LOD scores on the short arm of chromosome 8 with a maximum LOD score of 3.72 between markers ATAA018 and D8S1477. This region was further saturated with additional polymorphic markers from the Marshfield genetic map¹⁰. After saturation of this region, linkage was confirmed with a maximum LOD score of 4.09 (Figure 8.5).

Delineation of the candidate region

Pedigree and haplotypes were generated using the Cyrillic 2.1 software (Cyrillic Software, Oxfordshire, UK). The black haplotype is seen only in patients (Figure 8.4). Two additional individuals (IV.2 and IV.13) were analysed for this region. Their diagnosis was not clear at the time of the genome scan, but in the meantime it was confirmed that IV.2 is affected and IV.13 reached the age of 18 without any radiological abnormalities, so he is considered unaffected. Two recombination events delineate the region. At the distal side, there is a recombination proximal of marker D8S282 in individual II.1. At the proximal side a recombination occurs distally of D8S1809 in

individual III.7. This delineates the region to 12.13 cM (centiMorgan) or 6.65 Mb (megabases) and contains 100 genes according to the NCBI database (<http://www.ncbi.nlm.nih.gov/>).

However, if we look at individual IV.13, who has reached the age of 18 without abnormalities, and is therefore considered unaffected, there is a recombination between markers D8S1739 and D8S382. Hence, the proximal part of the black haplotype can be excluded. This would further narrow the region to 8.3 cM between markers D8S282 and D8S382. This region encompasses 4.35 Mb and contains 64 genes according to the NCBI database.

Selection and exclusion of candidate genes

The genes in the region were prioritised using Suspects and Endeavour¹⁴⁻¹⁶. Both systems prioritise candidate genes based on a training set of genes, in this case, *LRP4*, *LRP5*, *SOST* and *TGFB1*, since they are known to cause bone dysplasias with involvement of the skull. Interesting candidate genes in this region are *BMP1*, *LOXL2* and *ADAM28*. They are all ranked in the top ten of Suspects and Endeavour. *Bone Morphogenetic Protein 1 (BMP1)* is expressed in bone tissue and encodes a protein that is capable of inducing formation of cartilage. *BMP1* is not an authentic member of the BMP protein family but belongs to the astacin/BMP1/toloid (TLD)-like family of zinc metalloproteinases which are fundamental in the development and formation of the extracellular matrix¹⁷. *BMP1* has been suggested to play essential roles in osteogenesis and extracellular matrix formation. It exerts influence over dorsal-ventral patterning through the indirect activation of some TGF β -like proteins^{18,19} and is involved in the proteolytic processing of the procollagen I C-propeptide for the generation of mature collagen type I¹⁸. The BMP1-3 isoform of the *BMP1*-gene is significantly increased in patients with acute bone fracture and plays a critical role in bone fracture repair¹⁷. Mutations in *BMP1* cause autosomal recessive Osteogenesis Imperfecta^{18,20}. Homozygous *BMP1*^{tm1} mice, in which the *BMP1* gene has been disrupted by deleting DNA sequences encoding the active site of the astacin-like protease domain common to all splice variants, have defects in skull development. They show reduction in the size of the frontal, parietal and interparietal membrane bones of the skull. Besides skull defects there are no other skeletal abnormalities in these mice²¹.

LOXL2 is a member of the lysyl oxidase family. It is essential for the biogenesis of connective tissue, encoding an extracellular copper-dependent amine oxidase that catalyses the first step in the formation of crosslinks in collagens and elastin. A study exploring the potential direct effects of 1,25(OH)₂D₃ on the quality of collagen in an osteoblastic cell culture system showed that *LOXL2* was constantly and significantly upregulated by 1,25(OH)₂D₃. Although the function of *LOXL2* in osteoblasts is not yet known, it seems to play a role in 1,25(OH)₂D₃-induced collagen phenotypes²². *LOXL2* is also a major isoform in chondrocytes and is required for their differentiation.

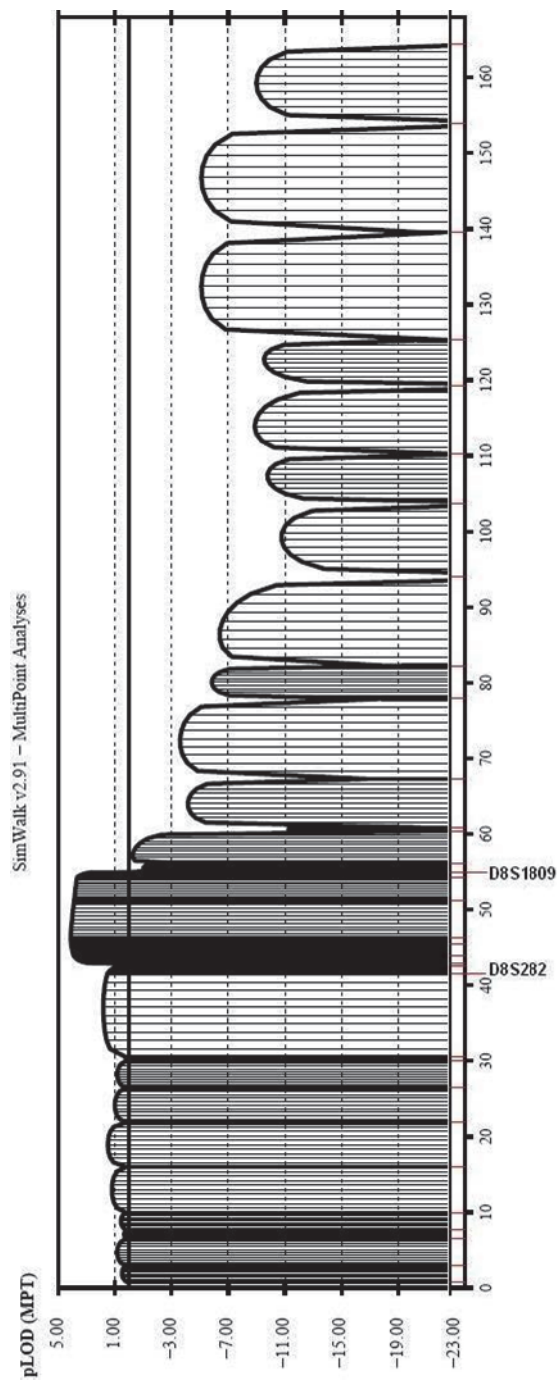


Figure 8.5 Multipoint LOD scores for chromosome 8, after saturation with additional markers, showing a maximum LOD score of 4.09 between markers D8S1734 and D8S1809.

The LOXL2 expression pattern in healing fractures and in developing growth plates indicates abundant expression in chondrocytes²³. Other members of the lysyl oxidase gene family may also play a role in bone homeostasis. Lysyl oxidase (LOX) catalyses cross-linking of elastin and collagen, which is essential for the structural integrity and function of bone tissue.

The expression of LOXL1-4 is significantly downregulated in bone tissue of LOX (-/-) mice²⁴.

ADAM28 is a member of the ADAM (a disintegrin and metalloprotease domain) family. There are no data available on the expression of this gene in bone tissue, nor is any function in bone metabolism known so far. However, it is an interesting candidate gene, since several other members of the ADAM family have been implicated in bone metabolism. Inactivation of *ADAM9* by MT1-MMP regulates FGFR2 signalling and calvarial osteogenesis. MT1-MMP cleaves *ADAM9* to protect FGFR2 from ectodomain shedding. Depletion of *ADAM9* in MT1-MMP-deficient mice significantly rescued the calvarial defects via restoring FGF signalling^{25,26}. Increased expression of *ADAM8* enhances osteoclast formation, differentiation, and bone resorption per osteoclast and results in osteopenia in vivo, whereas loss of *ADAM8* in vivo does not significantly affect normal bone homeostasis but blocks the osteoclast stimulatory effects of inflammatory cytokines such as TNF- α , which is a major cytokine implicated in inflammatory bone loss²⁷. *ADAM19* was suggestively associated with bone density in an extended genome-wide association study of bone mineral density among Icelanders and a follow-up study in subjects of European descents²⁸.

Sequence analysis of these genes did not reveal any mutations. To ensure that both copies of the gene are present and to rule out large deletions, SNPs were analysed. For each gene at least two heterozygous SNPs were found in patient IV.14 covering a major part of the genomic region of the gene (Table 8.1). This indicates that both copies of each gene are present.

Table 8.1 SNPs in *BMP1*, *LOX2* and *ADAM28* that were heterozygous in patient IV.14.

Gene	Number of exons	Intragenic polymorphisms	
		rs number	Position (NCBI build 37.3)
<i>BMP1</i>	20	rs67774528	Chr8:22035249:22035250 (intron 6-7)
NM_006129.4		rs4075478	Chr8:22053123 (intron 13-14)
<i>LOXL2</i>	14	rs3765215	Chr8:23160778 (intron 11-12)
NM_002318.2		rs2280936	Chr8:23155337 (3'UTR)
<i>ADAM28</i>	23	rs6996616	Chr8:24171051 (exon 6)
NM_014265.4		rs145612420	Chr8:24187586 (exon 11)
		rs2278467	Chr8:24188844 (intron 12-13)
		rs11994522	Chr8:24196898 (intron 14-15)
		rs7829944	Chr8: 24207399 (exon 19)
		rs7009516	Chr8:24208847 (intron 20-21)
	rs1058914	Chr8:24212040 (3'UTR)	

Discussion

Bone is constantly remodelled throughout life by bone formation and bone resorption. Normally, these processes are in balance. Disturbance of this balance can lead to different bone pathologies, with either increased or decreased bone density. Analysing families with an increased or decreased bone density can lead us to new genes involved in abnormal bone density. Identification of these genes can give new insights in the understanding of bone homeostasis.

Linkage studies have previously shown to be a successful way of identifying new genes in monogenic families. *SOST* was identified with positional cloning studies in families with Van Buchem disease⁷ and sclerosteosis⁹. In a kindred with High Bone Mass trait, *LRP5* was identified as the causative gene^{29,30}. Both genes are now known as important elements of the Wnt/ β -catenin pathway.

HCI is a sclerosing bone dysplasia of the skull. Besides HCI, numerous sclerosing bone dysplasias with involvement of the skull exist, for example Van Buchem disease, sclerosteosis and Camurati-Engelmann disease. Van Buchem disease (OMIM 239100) and sclerosteosis (OMIM 269500) are both autosomal recessive disorders with similar clinical features like hyperostosis of the skull, mandible, clavicles, ribs and tubular bones. A typical feature is the enlarged mandible which is seen in most patients. The difference between Van Buchem disease and Sclerosteosis is that in the latter, patients show excessive height – sometimes even gigantism – and hand abnormalities^{31,32}. This is absent in patients with Van Buchem disease. A 52 kb (kilobases) deletion located downstream of *SOST* is found in patients with Van Buchem disease³³, whereas sclerosteosis is caused by missense mutations in *SOST*³⁴. Mutations in *LRP4* were identified in two isolated sclerosteosis-2 cases (OMIM 614305)³⁵. Camurati-Engelmann disease (CED) also belongs to the group of craniotubular hyperostoses and is characterised by cortical thickening of the diaphyses of the long bones. Sclerotic changes at the skull base can occur as well. CED is caused by mutations in *TGFB1*^{8,36}. Finally, missense mutations in *LRP5* were found in several High Bone Mass syndromes^{29,37,38}.

We were able to exclude all these genes mentioned above based on LOD scores below -2, indicating there is no linkage between the phenotype and the chromosomal regions of these genes. Exclusion of these genes was not entirely unexpected since the whole skeleton is affected in these disorders whereas in HCI only the skull is affected.

We located the disease-causing gene for HCI in a 8.3 cM region on chromosome 8. This region encompasses 64 genes of which very few have a known function in bone metabolism. The region was delineated by two important recombination events. At the distal side, a recombination occurred proximal of D8S282. At the proximal side, a recombination occurred between D8S1739 and D8S382 in IV.13. This recombination can further narrow the region, and although this individual is considered healthy because he reached the age of 18 without any symptoms or radiological abnormalities,

we will have to keep in mind that he is still young. We focused in our study on the 8.3 cM region, but keep in mind that it is possible that the disease causing gene might be in the larger 12.13 cM region.

Genes were prioritised by Endeavour and Suspects. Suspects matches Gene Ontology terms, InterPro domains, and gene expression data built on top of the PROSPECTR candidate prioritisation system, which uses sequence features to rank genes in order of their likelihood of involvement in disease. Suspects drills down further to rank genes involved in specific complex traits and syndromes¹⁴. Endeavour matches candidate genes with training genes based on functional annotations, protein-protein interactions, regulatory information, expression data, sequence-based data and literature-mining data^{15,16}. *BMP1*, *ADAM28* and *LOXL2* were the most interesting candidate genes, based on their ranking by Endeavour and Suspects, their expression in bone tissue and their function. Sequence analysis of these three genes did not reveal any mutations and SNP analysis ensured the presence of both copies of the genes. *ADAM28* is relatively well covered by heterozygous polymorphisms. This is less the case for *BMP1* and *LOXL2*. Therefore, we cannot exclude small deletions only affecting a few exons in the latter genes. These results suggest that a gene not previously known in bone metabolism will be responsible for hyperostosis of the skull in this family. This could be a gene that shows specific expression in skull bones. Another possibility is a gene that is expressed in neighbouring tissues, which this way influences the metabolism of the adjacent skull bones. Further sequencing of genes in the region should be performed. Since there are still many genes in this region, exome sequencing could be considered since the combination of linkage studies with exome sequencing can lead to identification of new genes and gene pathways in bone formation³⁹.

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Part IV

Casuistics

Chapter 9

Facial nerve decompression via middle fossa approach
for hyperostosis cranialis interna is feasible

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Abstract

Hyperostosis cranialis interna (HCI) is an autosomal dominant disorder characterised by endosteal hyperostosis and osteosclerosis of the skull base and calvaria, leading to compression and dysfunction of cranial nerves I, II, VII and VIII. We report on bilateral surgical decompression of the internal auditory canal in HCI. An eight year old girl presented with bilateral facial palsy due to HCI. Via a middle fossa craniotomy both internal auditory canals were unroofed and the cranial nerves VII and VIII were decompressed. The mimic function recovered and one year post-operatively House-Brackmann grade I and II respectively were observed. Concluding, this is the first report on surgical decompression of the internal auditory canal in HCI. Surgical decompression of the internal auditory canal is recommended therapeutically, but may also be performed prophylactically in younger patients with HCI.

Introduction

Hyperostosis cranialis interna (HCI) is a disorder that is characterised by hyperostosis and osteosclerosis limited to the calvaria and skull base. This leads to narrowing of cranial nerve foramina and hence cranial nerve entrapment, mainly of cranial nerves I, II, VII and VIII. Smell, taste and vision impairment, facial palsy and vestibulocochlear dysfunction may occur at young age. Besides, increased ocular and intracranial pressure can occur. HCI has an autosomal dominant transmission pattern and was first described in 1990¹.

Craniofacial hyperostotic disorders can lead to dysmorphic, functional and neurological symptoms. No causal treatment modalities are known. Symptomatic treatment can exist of cranial vault decompression² or cranial nerve decompression. Successful vestibulocochlear and optic nerve decompression have been described in other craniofacial hyperostotic disorders³⁻⁵.

In this report we like to communicate our experience, the technique and functional outcome of the first (bilateral) surgical decompression of the internal auditory canal (IAC) via middle fossa approach in a patient with facial palsy due to HCI.

Case report

An 8-year-old girl presented with sudden paresis of the left side of the face evolving to a paralysis within 2 days (House-Brackmann grade VI). The referring otolaryngologist prescribed antibiotics and steroids. Her left-sided paralysis partially resolved after treatment with antibiotics and prednisolone, House-Brackmann (HB) grade III. Her medical history was uneventful. There was a remarkable family history of facial palsy due to HCI. The facial appearance was otherwise normal. The otoscopic aspect of the eardrums was normal, there was no impairment of other cranial nerves and the ophthalmologic examination was normal.

Audiometry revealed normal hearing levels. The stapedial muscle reflex was absent at the left side. Vestibular examination and brainstem audiometry were normal. Routine laboratory investigation revealed no abnormalities.

Radiological imaging by means of computed tomography (CT) was performed. Bilaterally, the middle and the medial part of the IAC were narrowed (Figure 9.1A and 9.11B) down to 2-3 mm. The middle and inner ear displayed no abnormalities. The skull showed diffuse hypodense hyperostotic areas and a hypodense enlarged endosteal cortex of the greater wing of the sphenoid bones and the petrous bones (Figure 9.2). The calvaria were not enlarged. Magnetic resonance imaging (MRI) revealed no supplementary information.

Clinical symptoms, findings and imaging results confirmed the diagnosis HCI. The facial nerve function did not further recover. Because of the age of the patient and the

knowledge that at older age osteosclerosis may progress along with deterioration of facial nerve function, it was decided to discuss with the parents a surgical decompression of the facial nerve via a middle fossa approach. The parents gave consent.

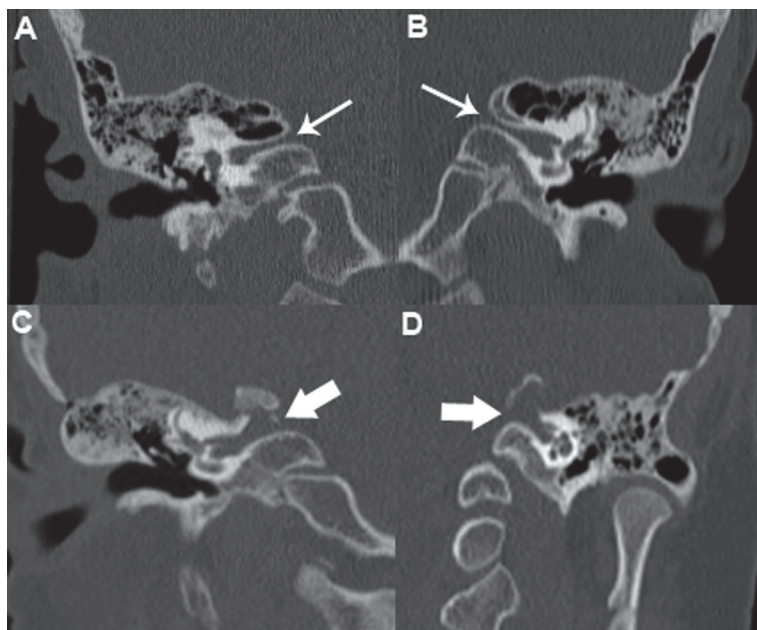


Figure 9.1 Sagittal reconstructions, the internal acoustic canal is indicated with arrows. (A) pre-operatively right, (B) pre-operatively left, (C) post-operatively right, (D) post-operatively left.

Ten months after the initial left paralysis she developed a sudden right-sided facial palsy. ENT-examination revealed a partially recovered left facial palsy HB grade III and a right facial palsy HB grade VI (with absent stapedial muscle reflex), whereas all other investigations remained normal. Treatment with prednisolone resulted in a partial recovery (HB grade IV).

The patient was scheduled for surgery at the right side first; it was argued that a shorter period of impairment may increase the chance of recovery. One year later the left side was operated, which had remained HB grade III.

The surgical procedures were performed with the head fixed in the Mayfield frame. Routine monitoring of facial nerve function (NIM-2[®] XL Nerve Integrity Monitoring System, Medtronic, Minneapolis, USA) and of hearing by auditory brain stem response monitoring were used throughout the operation. A neuronavigation system was used (Medtronic Surgical Navigation Technologies, Louisville, Colo., USA). Cranial to the ear, an inverted v-shaped incision was made. The temporal muscle was split in an inverted

T-shape. Through a 5x3 cm trepanation and elevation of the dura mater the middle fossa was approached. The superior petrosal sinus and the cranioposterior petrosal bone were identified. The routine landmarks to identify the position of the IAC could not be applied. Especially the subarcuate eminence, or the greater superior petrosal nerve (GSPN) could not be found. The superior semicircular canal lay buried under an abnormally thickened layer of bone which contained several large cells. The IAC was identified at the bottom of one of these cells. The consistency and aspect of the bone was normal. The IAC was pear-shaped with its narrowest point medially. The superior and the medial part of the IAC were drilled thin and subsequently removed.



Figure 9.2 Coronal CT-scan at the level of the sphenoid bone and middle skull base displaying diffuse abnormal findings. There is marked increased endosteal bone formation of the squama temporalis and the corpus temporalis bilaterally (arrows). The arrowheads indicate hyperostosis of the petrous bone.

During the *first* operation (right side) the nerves of the IAC were found to blossom out into the overlying air cells. A small defect in the posterior fossa dura was repaired with a free muscle graft and fibrin glue (Tissuecol®, Baxter, Deerfield, IL., USA). A lumbar drain was placed for a few days. The facial nerve function was HB grade IV pre- and post-operatively and was completely restored (HB grade I) one year after the operation.

The contralateral side was operated one year later. During this similar procedure, at the time of opening the IAC, the facial nerve bulged out instantly. This normalised after administration of 4 mg intravenous dexamethasone. One year after each operation the right and left facial nerve function were restored to HB grade I and II respectively. Post-operative CT-scans revealed a significantly enlarged medial IAC bilaterally (Figure 9.1C and 9.1D).

Discussion

In our patient with HCI, a marked medial IAC stenosis was present bilaterally, whereas the lateral IAC, the labyrinthine, the tympanic and mastoid segments of the Fallopian canal were normal. This justifies exploration of the middle and medial IAC only. Furthermore, exploration of the unaffected lateral IAC would superimpose the unnecessary risk of damaging the facial nerve and the labyrinth. Both surgical decompressions had the desired effect: nearly complete recovery of the facial nerve function. The decision to perform the surgical decompression was based on the following arguments: the early age of symptomatic HCI and the assumption that at older age the osteosclerosis increases, as is seen in several other family members. A bilateral palsy occurred in four other family members when nerve monitoring was not yet available. Their facial nerve functions never recovered after conservative treatment. Reports on decompressive facial nerve decompressive surgery for cranial hyperostotic disorders *via middle fossa approach* have only been published scarcely. Thorough analysis of the literature reveals eight reports. Hamersma mentions four cases of labyrinthine and meatal decompressions in sclerosteosis (by Hamersma, Fisch and House)⁶. Miyamoto et al. report this procedure in two patients with Camurati-Engelmann disease⁷. Benecke et al. report a successful total facial nerve decompression in a patient with Camurati-Engelmann disease and a middle fossa approach for decompression of the IAC and labyrinthine segment in a 3-year old boy with recessive osteopetrosis⁸. Based on their experiences and observations of (intracranial) complications, the authors conclude that facial nerve decompression should be avoided in such severe cases. Tibesar et al. report on IAC decompression via middle fossa approach for sensorineural hearing loss due to vestibulocochlear nerve encroachment in a patient with Camurati-Engelmann disease⁹.

Two mechanisms can be thought of to cause the facial nerve dysfunction. First, the direct compression of the nerve by progressive hyperostotic changes of the skull base and its neuroforamina, and second, the impairment of the perineural microvasculature. The reversibility of the cranial nerve function of our case suggests an important role of the latter mechanism: (transient) ischaemia leads to facial nerve oedema.

Although HCI is a rare disorder, this procedure can be thought of in other hyperostotic craniofacial disorders, like osteopetrosis, osteopathia striata, Camurati-Engelman

disease, craniodiaphyseal disease, Lenz-Majewski syndrome, Van Buchem disease, sclerosteosis and craniometaphyseal dysplasia¹⁰.

Conclusion

In our patient IAC decompression has shown to be effective in reversing facial nerve dysfunction due to encroachment in a patient with HCI. The varying manifestations of HCI and the lack of prognostic factors indicating progression of disease make it difficult to predict the clinical course. However, based on experience with other patients with facial nerve paralysis due to HCI we do not expect the facial nerve function to improve with conservative treatment only. These findings plea for surgical decompression at early age. Moreover, in patients without pronounced hyperostosis and osteosclerosis of the skull, the operative landmarks are still recognisable. Therefore in young patients with HCI, in which progressive hyperostosis is to be expected, prophylactic surgical decompression of a narrowed IAC can be considered.

Summary

HCI is a disorder that is characterised by hyperostosis and osteosclerosis limited to the calvaria and skull base. This leads to narrowing of cranial nerve foramina and hence cranial nerve entrapment, mainly of cranial nerves I, II, VII and VIII.

In this patient with HCI there was an isolated bilateral stenosis of the medial internal auditory canal. Facial nerve decompression via middle fossa approach can be successfully performed in patients with cranial nerve entrapment due to a hyperostotic and narrowed IAC. Despite the technical advances of surgical decompression of the IAC, it is considered advisable in patients without pronounced hyperostosis and osteosclerosis of the skull when the operative landmarks are still recognisable.

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Chapter 10

Cerebral vasospasm after auditory brainstem
implantation in a patient with hyperostosis cranialis
interna

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Abstract

Hyperostosis Cranialis Interna (HCI) is a hereditary bone dysplasia with autosomal dominant transmission pattern characterised by progressive hyperostosis and osteosclerosis of the cranial vault and the skull base (MIM 144755). Encroachment of neuroforamina causes function loss of cranial nerves I, II, V, VII and VIII. We present a 44-year-old female with bilateral sensorineural deafness caused by HCI in whom an auditory brainstem implant was placed for auditory revalidation via retrosigmoidal approach. Although the auditory result was satisfactory, this procedure was complicated by neurological deficit caused by postoperative cerebral vasospasm. To our knowledge this is the first report of a postoperative cerebral vasospasm after this procedure. This report discusses the possible aetiology of this complication and offers suggestions in performing auditory brainstem implantation in a novel candidate population of patients with hyperostotic skull disorders.

Introduction

Auditory brainstem implantation (ABI) is indicated in case of bilateral neural deafness. The majority of the patients suffers from bilateral vestibular schwannomas related to neurofibromatosis type 2¹. Possible other indications for ABI are bilateral severe ossification of the cochlea due to otosclerosis, cochlear obliteration due to meningitis, cochlear aplasia and traumatic cochlear nerve avulsion². ABI can also be considered in case of bilateral vestibulocochlear neuropathy in patients with craniofacial hyperostotic disorders, such as Camurati-Engelmann disease, sclerosteosis, osteopetrosis and craniometaphyseal dysplasia. HCl is such a hyperostotic hereditary disease characterised by endosteal hyperostosis and osteosclerosis of the cranium and the skull base and to a minimal extent also the mandible (MIM 144755)³. The transmission pattern is autosomal dominant. Patients are affected to a different extent. Skull base hyperostosis causes cranial nerve entrapment (I, II, V, VII and VIII) due to narrowing of their foramina. Hyperostosis of the cranial vault is most profound in the frontal and temporal regions. Severe hyperostosis causes reduced space in the pontocerebellar cistern and can eventually cause brainstem compression.

Patients generally become symptomatic in the second decade or late in the first decade. Facial palsy and vestibulocochlear impairment are often the first symptoms due to encroachment of the medial part of the internal auditory canal. Symptomatic patients are best treated by (sub)acute decompression of the internal auditory canal⁴, possibly followed by cochlear implantation. However, in case of prolonged existing profound sensorineural hearing loss due to advanced hyperostosis and osteosclerosis of the skull base and an obliterated internal auditory canal, an auditory brainstem implant can be considered. To our knowledge, this is the first report on auditory brainstem implantation in a patient with skull base hyperostosis.

Case report

The proband is a 44-year-old woman with HCl. Multiple cranial nerve entrapment due to hyperostosis has caused progressive functional losses: around the age of 10 she presented with bilateral successive facial nerve palsies. In her early 20s, a right-sided sudden deafness occurred (typically during pregnancy; hormonal influences are often seen in HCl, presumably perineural oedema causes sudden nerve entrapment), whereas her left-sided deafness was slowly progressive. She underwent right optic nerve decompression at the age of 37 because of deteriorating vision with pre-existing optic neuropathy. Her senses of smell and taste are completely lost. Moreover, she suffers from episodes of stabbing headaches.

Funduscopy revealed optic atrophy at the right side and no abnormalities at the left side. Ocular pressure was 16 mmHg at the right and 24 at the left side. Facial nerve

function was scored as grade 4 at both sides according to the House Brackmann scale. Pure tone audiometry revealed complete bilateral deafness. Otoacoustic emissions were absent. Calorisation of the vestibular apparatus showed bilateral areflexia of the lateral semicircular canals.

Computed tomography revealed profound endosteal hyperostosis and osteosclerosis of the calvaria and the base of skull. The porus of the internal auditory canals were obliterated. The labyrinth and the middle ear were not affected. Additional magnetic resonance revealed obstruction of the cerebellopontine cisterns and a decreased amount of cerebrospinal fluid surrounding the brainstem at the level of the foramen magnum and the posterior fossa (Figure 10.1).

It was decided to place an auditory brainstem implant for auditory rehabilitation, because of severe communicative impairment. The procedure was performed at the left side because the duration of auditory deprivation at this side had been shorter.

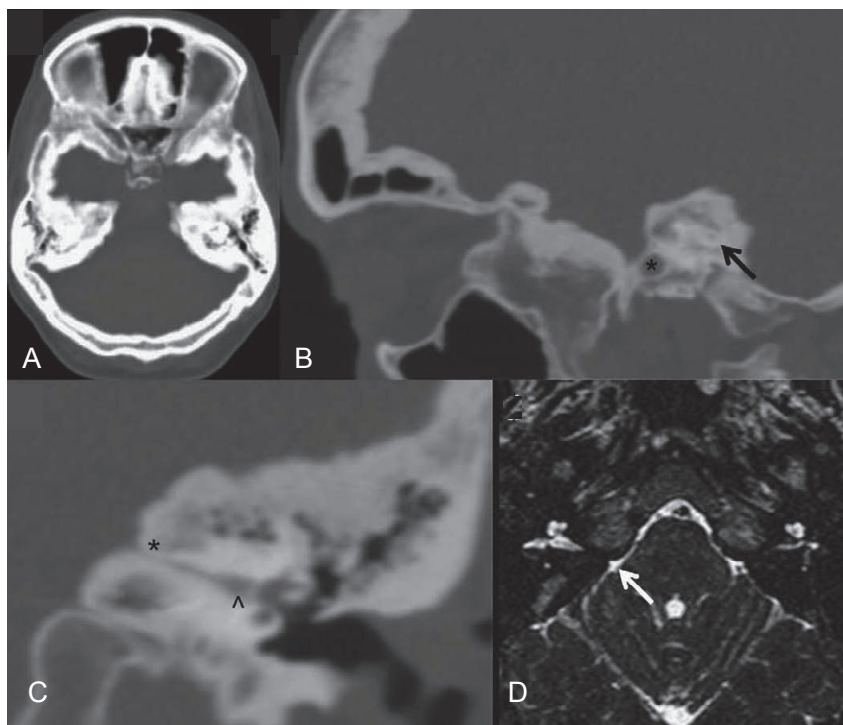


Figure 10.1 (A) Preoperative axial CT image: remarked endosteal hyperostosis of the petrous bone and the skull surrounding the temporal lobes, as well as the ethmoid area. (B) Sagittal reconstruction of the right middle and frontal skull base. The arrow indicates the former internal auditory canal. The carotid artery (asterisk) is not affected. (C) Coronal reconstruction of the left internal auditory canal, showing a patent fundus (arrow head) and stenotic porus at its maximal diameter (asterisk). (D) T2-weighted axial MRI image: obliterated internal auditory canal (arrow) and limited space for cerebrospinal fluid surrounding the brainstem and the cerebellum.

Intervention

During the procedure, facial nerve and glossopharyngeal nerve function monitoring were used (NIM-2[®] XL Nerve Integrity Monitoring System, Medtronic, Minneapolis, USA), as well as neuronavigation (Medtronic Surgical Navigation Technologies, Louisville, CO, USA).

A retrosigmoidal approach was used. The dura was very adherent to the thickened skull, causing some bleeding from the sigmoid sinus which could easily be stopped. Subsequently, the arachnoid was opened and the cerebellum was retracted. The basal cistern was opened leading to optimal exposition of the extremely narrow cerebellopontine angle. The medial part of the internal auditory canal could be identified, using the neuronavigation. The vestibulocochlear, facial and lower cranial nerves were identified. There was no excessive blood loss. A Nucleus 24 ABI[®] (Cochlear™, Sydney, AUS) was inserted into the lateral recess of the fourth ventricle adjacent to the dorsal cochlear nucleus with good intraoperative electrically-evoked auditory brainstem responses.

Postoperative course

Immediately postoperatively the patient reported increased headache and nausea which improved after the administration of dexamethasone. Discharge followed one week postoperatively in a fair to good overall clinical condition. However, ten days postoperatively, she developed a state of confusion, agitation and impaired coordination. There was disorientation in time, place and person. Photophobia and meningismus were present. Further neurological examination revealed a left-sided Babinski plantar response. A CT scan revealed generalised cerebral oedema. Furthermore, bifrontal and biparietal hypodense areas and focal patchy enhancement after intravenous contrast administration were seen (Figure 10.2). The differential diagnosis was meningitis, cerebritis or diffuse infarction. There is no suspicion for sinus thrombosis or subarachnoidal haemorrhage.

Two weeks postoperatively she develops a paralysis of the right leg and a paresis of the right arm (grade IV) along with urinary incontinence. Because of these sudden focal neurological symptoms, cerebral vasospasm is considered clinically. Headache, lethargia, disorientation and meningismus supported this diagnosis. MR angiography was relatively contraindicated because of the brainstem implant and would cause major artifacts due to the magnet. CT angiography was performed. The hypodense areas were unchanged. The circle of Willis and the anterior and medial cerebral arteries were very thin and fragile, compatible with diffuse cerebral vasospasm (Figure 10.3). There seemed to be a combined anterior (ACA) and middle cerebral artery (MCA) syndrome, leading to incontinence and confusion (ACA) and paresis (MCA). Transcranial Doppler was impossible due to the thickness of the skull. The patient was treated with nimodopine and hypertensive treatment (volume expansion and catecholamines).

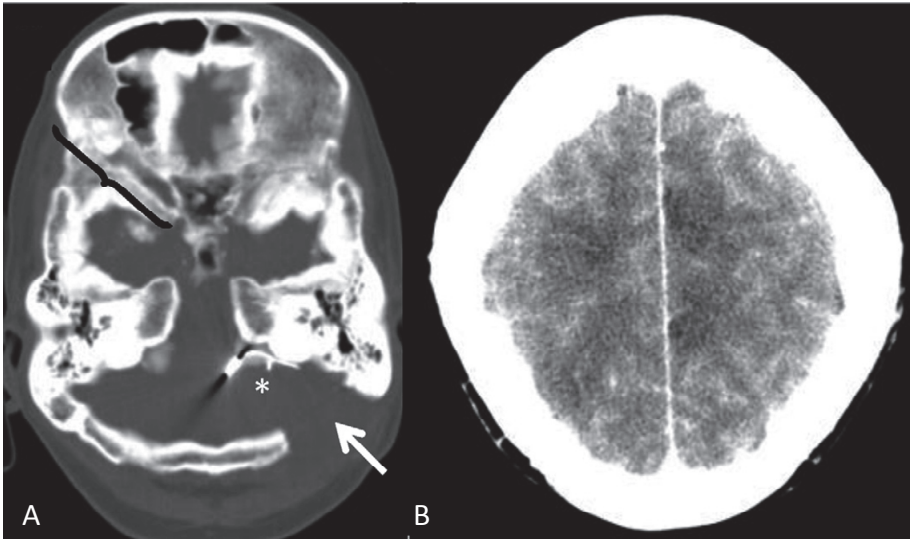


Figure 10.2 (A) Postoperative CT scan of ABI (asterisk) and the retrosigmoidal trepanation (arrow). The brace demonstrates the operation defect of the optic canal decompression. (B) Patchy cerebral enhancement with hypodense parietal areas.

Due to the intensive physical rehabilitation the first fitting session was postponed for 2 months. Out of 21 electrodes, 4 electrodes caused a pure somatosensory response, 2 caused an unpleasantly loud auditory response, and 5 caused a mixed auditory and somatosensory response at higher stimulation levels. 10 electrodes with various pitch and loudness levels were switched on.

One year after the incident, independent walking was still impossible and fine motor skills of the upper extremity were limited. The results of the auditory implant are subjectively excellent, and objectively good. Six months after implantation free-field tone thresholds are 40dB. She scored 60 to 85% on a close-set speech test and is reluctant to remove the speech processor at night.

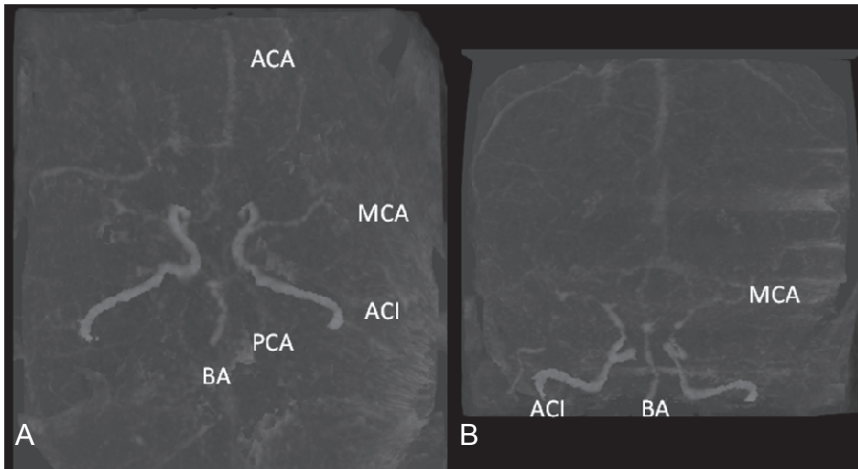


Figure 10.3 Postoperative transversal (A) and coronal (B) CT arteriographic 3D-reconstruction of the intracranial arteries. In contrast to the internal carotid arteries (ACI) and the basilar artery (BA), the middle cerebral (MCA) and the anterior cerebral arteries (ACA) have a smaller calibre than expected suggesting cerebral vasospasms.

Discussion

In this paper we report on diffuse cerebral vasospasm after auditory brainstem implantation for the first time in literature. Cerebral vasospasm occurs most frequently as a result of subarachnoid haemorrhage (SAH), usually between 6 and 8 days after haemorrhage⁵. The presence of vasoactive blood substances and nitric oxide in the basal cisterns are thought to enhance vasospasms in the case of SAH⁶.

Cerebral vasospasm after intracranial surgery is a very rare complication, of which the exact pathogenesis is only partially understood. Hypotheses of risk factors are postulated in an extensive review by Almubaslat⁷. Vasospasm after tumour resection has been reported after craniopharyngioma resection⁸, transsphenoidal hypophysectomy⁹, vestibular schwannoma and cranial base (posterior fossa) meningioma resection^{10,11}. In a large retrospective study of 470 cranial base tumour resections, cerebral vasospasm was reported 9 times, an incidence of 1.9%¹².

Risk factors can be roughly divided into *mechanical* or *biochemical* aetiology. *Mechanical* risk factors were found to be large tumour size, extensive operative time and vessel encasement¹³. Direct vascular damage to the arterial wall during surgery, mainly in (supra)sellar surgery is postulated¹³. Possible *biochemical* aetiologies of vasospasm after brain surgery are partially analogous to the pathogenesis of vasospasm after SAH (blood products in the basal cisterns). Moreover, liberation of vasoactive substances during intracranial tumour removal^{14,15} and a disturbed level of

catecholamines after pituitary or hypothalamic surgery¹⁶ are mentioned as causative factors. The stress of surgery in general is supposed to change the vascular tone due to prostaglandins, although this evidence is not strong¹⁷. A delayed onset of vasospasm after mechanical stress can be caused by chemoactive substances released by the surrounding tissue¹⁸.

The reason for postsurgical vasospasm presented in this report is peculiar because the operation is not in proximity of the suprasellar area. There has been no intraoperative cisternal bleeding. The craniotomy in our severe hyperostotic patient mimics a decompressive craniotomy, causing significant tissue shifting. Intracranial pressure changes occur along with changes in vascular tone. This change in vascular tone could be responsible for vasospasm induction. Furthermore, analogous to decompression of Chiari-I malformation, there is a sudden increase of cerebrospinal fluid (CSF) velocity as well as intracranial compliance because the cisterns are not longer obstructed^{19,20}. Although in our patient the intracranial pressure is not quantified (lumbar puncture is contraindicated due to the risk of brainstem herniation), intraoperative findings suggest increased pressure due to the hyperostotic skull. An impressed dura mater and bulging of the cerebellum after opening the dura mater were observed.

Cerebral vasospasm has never been published after craniotomy of a severe hyperostotic skull nor after auditory brainstem implantation before. This complication should be suspected in case of delayed deterioration of the neurologic condition of a patient, particularly with coexistence of focal neurologic deficits. Upon planning surgery, one must be aware of the distorted anatomy in a patient with a hyperostotic skull and of the changes that occur in CSF dynamics after decompression of the brain. If, in the future, we were to perform a retrosigmoidal craniotomy in such a patient, we would consider closing the craniotomy without the trepanated skull. A retrosigmoidal approach has been chosen to maximise exposition of the pontocerebellar cistern and to perform optimal decompression. Although generally retrosigmoidal and trans-labyrinthine approach have equal results, in this case a translabyrinthine approach would not have caused unnecessary cerebellar traction, whereas the afunctional inner ear structures can be sacrificed without consequences. In advance we had waived the option to perform a cochlear implant, because of the longstanding complete function loss of both the vestibular and cochlear nerves. Prior to cochlear implantation, decompression of the internal auditory canal via middle fossa approach would have been necessary. One could argue that internal canal decompression could have been favourable for the facial nerve as well and – if cochlear implantation would not have led to a satisfactory audiological result – auditory brainstem implantation would still have been possible. Promontory tests could have been useful to choose between auditory brainstem or cochlear implantation after internal auditory canal decompression. There is one report about successive internal auditory canal decompression and cochlear implantation in Camurati-Engelmann disease, however the patient still had minimal residual hearing a normal facial nerve function²¹.

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Part V

General discussion, summary and addendum

Chapter 11

General discussion, conclusions and future perspectives

General discussion and conclusions

Concerning pathogenesis

The unique feature of hyperostosis cranialis interna (HCI) is that there is intracranial hyperostosis and bone alteration only in the skull base and the calvarial bones and, to a lesser extent, in a localised area of the mandible. The rest of the skeleton and even the rest of the facial bones are not affected. There can only be speculated about the pathogenetic mechanism until the exact genetic and molecular basis of the disease have been uncovered. In some way processes must be going on in this areas of bone or adjacent tissue which do not occur elsewhere in the human body. In chapter 2 the embryology of the skull and skull base are discussed with emphasis on the type of bone formation, endochondral and intramembranous ossification. It seems logical to suspect a defect in one of these mechanisms, however they are both affected – so indirectly it can be concluded that there is no direct causal relationship with the type of ossification. One can look at ossification – and a defect mechanism of it – from another perspective: bone grows, remodels and regenerates in function of growth factors. The most important growth factors for bone are the bone morphogenetic proteins (BMPs). BMPs belong to the transforming growth factor β superfamily. BMPs play an important role in the embryonic development of bone, postnatal growth and adult remodelling of bone¹. Involvement of BMP1 – one BMP in the candidate region has been excluded (chapter 8)².

The expression of the growth factors is different in various parts of the skull and is also different during different stages of development. A lot of research on this subject has been performed after it has been observed that juvenile mammals (also humans) are able to regenerate calvarial defects, whereas adult animals lack this capacity. The first report on this topic was already published in 1979^{3,4}. Many substances of the healing calvarial complex have been suggested ever since as being important regulators of this age-related difference in regenerative capacity. Examples of growth factors that were found in altered concentrations in juvenile calvaria are Runx2, BMP-2, BMP-4, BMP-7 and pleiotrophin⁵⁻⁷.

Mabbutt demonstrated in 1979 that regeneration of calvarial bone not only occurred from the margins, but also newly deposited bone appeared in the middle of the calvarial defect of the neonatal rabbits⁴. This suggested – apart from the regenerating capacity of neighbouring bone – also bone regeneration capacity of other adjacent structures (Figure 11.1). A regulatory role for the dura mater and the pericranium was proposed. A defect in this mechanism could play a role in the pathogenesis of HCI, however some affected structures (mandible, stylomastoid process) are not adjacent to the dura mater at all.

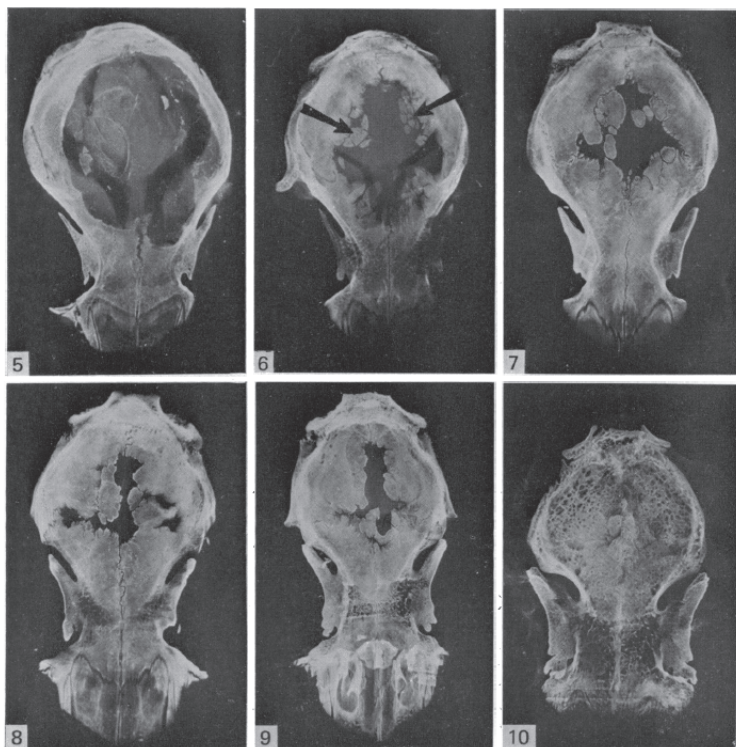


Figure 11.1 Radiographs from Mabbutt's study in 1979 of craniectomised neonatal rabbits showing gradual osteoneogenesis from both the dissection margins as well as adjacent to the margins⁴. Photo 6 = at 2 weeks, photo 8 = at 8 weeks, photo 9 = at 12 weeks and photo 10 = at 26 weeks.

In 1981 Takagi demonstrated that iatrogenic calvarial defects in rats, not healing spontaneously, healed after being filled with a bovine BMP fraction (note: different types of BMP were not yet discovered at that time)⁸. Again, there was not only ingrowth from the bony edge of the trepanation, but also proliferation of perivascular mesenchymal-type cells (pericytes) of the dura mater. Under the influence of BMP, dural pericytes differentiated into chondroid and woven bone. Similar studies in the 80s have been performed in monkeys, sheep and dogs⁹⁻¹¹.

A defect in one of the regulatory mechanisms of bone differentiation/growth in the skull seems plausible in the case of HCl. This mechanism could either be paracrine (cell reaction to a locally increased concentration of a substance) or juxtacrine (contact-dependent signalling).

Concerning clinical care

Diagnosis

(Family) history, physical examination

There is a reason for each doctor's visit. Recurrent and especially familial occurring facial palsy should draw attention to HCI or another (skull base) bone dysplasia. All cranial nerves should be tested in this case, of course also in the light of other diseases in the differential diagnosis. In case of familial occurrence, the age of onset, variance of severity and sex differences should be asked for to get an idea of possible inheritance pattern and possibly incomplete penetrance.

Dozens of causes of (bilateral or recurrent) facial palsies have been reported (see overview in the article of Oosterveer and also in the introduction of this thesis¹². However, often the palsy remains idiopathic in many patients who have recurrent facial palsy (84%)¹³ or bilateral facial palsy¹⁴. There have been studies about familial clustering of Bell's palsy¹⁵⁻¹⁸. Serology of neurotropic pathogens should definitely be investigated in every case.

Imaging and skeletal survey

Imaging is indicated in case of deterioration of the palsy despite treatment with steroids and in case of recurrent and familial facial palsy. CT imaging is the gold standard in case structural bone abnormalities are suspected. MR imaging shows possible neuritis, neural oedema, soft tissue abnormalities or osteomyelitis. In case of (suspicion of) a bone dysplasia a complete skeletal survey is mandatory, also in children.

The calvarial and skull base abnormalities will not be discussed again as they have been extensively discussed in chapter 5. The changes in the mandible, detected during the radiological study, deserve some attention here. They have been observed in all adult patients of the family (except for one, of whom CT images of the mandible are not available, individual III-1), whereas (affected) children and unaffected adults do not have any mandibular abnormalities. It is tempting to involve this torus mandibularis in the phenotype of HCI, especially because unaffected family members do not display this variant.

However, torus mandibularis (and also torus palatinus) do also exist as an anatomical variant on its own, sometimes in hereditary form^{19,20}, with a prevalence of approximately 15% and even much higher in certain ethnic groups, up to 68% in Icelanders and 85% in Inuit^{19,21,22}, almost never in children²². Torus mandibularis is described as cortical exostoses formed by dense cortical and limited amount of bone marrow, located on the internal side of the horizontal branch of the mandible, above the mylohyoid line and at the level of the premolar or the canine area (which is the case

in HCl)²³. It has been proposed that these exostoses occur by osteogenesis due to the stimulation of dormant osteoblasts and pluripotential cells from the inner layer of the periosteum after microtrauma of the periosteum^{24,25}.

Genetic testing

Even though the diagnosis can be established by CT once abnormalities become visible, it is also possible to set the diagnosis with genetic testing, since the discovery of the disease-causing region on chromosome 8p21 and more specifically since the detection of the mutation in the *ZIP14* gene, which is most probably responsible for the disorder. Genetic testing can be important, for example, for counselling reasons or if there is uncertainty about the diagnosis upon CT images. In general, genetic testing in asymptomatic patients is not favoured, for the simple fact that a positive diagnosis makes the subject a patient all of a sudden. Parents, however, often insist on knowing the faith of their child. Besides, early diagnosis in the presymptomatic phase gives more time to prepare the parents on the major implications and possible surgical interventions that might follow. This is a typical example of tailored medicine which has to be done in dialogue with the patient and/or the parents.

Genetic testing during pregnancy would also be possible, however this has not yet been performed. All patients of the family have been informed about this possibility. We have discussed the ethical aspects of this possibility with the colleagues of the Department of Genetics in the Maastricht University Medical Center. The preliminary conclusion is that before any type of invasive testing is to be performed, extensive counselling of the parents by both geneticist and physician would have to take place. The parents have to be informed extensively about the burden of a child with this disorder, and at the other side the capacity of the parents to deal with the possibly related problems in case their child is affected needs to be assessed. Also if prenatal diagnostics are considered (i.e. amniocentesis), obviously the goal and the potential risks of the procedure should also be discussed by the geneticist.

Treatment

Of course, one of the goals of this thesis is to elaborate possible treatment options in order to be able to support and counsel the affected patients. Unfortunately, the section with possible treatment options for this disorder is limited. Treatment cannot be standardised due to the different course and severity of the disease in different patients. We do think that centralising care for the patients and check them regularly is one of the key points we have learned. Patients become familiar with the disease, get educated about important symptoms and on the other hand, the doctors get insight in the course of a particular individual. The physician can gradually inform the patient and prepare for what might be coming in the future.

Until now, treatment is only supportive and symptomatic. Since the detection of the area of the genetic defect it is possible to diagnose the disease with certainty in the

presymptomatic period. In our experience, the parents greatly appreciate the possibility to be informed about this. We provided ample counselling to the parents after the diagnosis was made. Information about anatomy, possible related symptoms, the need for regular check-up as well as imaging and possible treatment options gives parents and patients insight in the disease.

The most common presenting symptom is facial nerve palsy, generally occurring in the first or second decade. This has a very high impact on both the patient as well as parents. Initial treatment with steroids is indicated to decrease what is thought to be perineural oedema. Imaging should then give insight in the exact location of facial nerve compression. Compression in the first intratemporal part of the facial nerve is observed most often, more specifically the porus of the internal auditory canal. If the skull base anatomy is not too much distorted, internal auditory canal decompression is a good option and facial nerve function recovery is observed in our case (chapter 9). If hearing deterioration due to porus compression would be the first presenting symptom, the same treatment would be suitable. We have one case of (left) facial palsy in a 5-year-old girl with only minor abnormalities at the level of the skull base. Probably the compression takes place in the labyrinthine part of the facial nerve (osteosclerosis in this area); the child has normal hearing. It was considered too dangerous for the hearing to decompress the nerve in this part.

Nerve compression in the third part of the intratemporal course of the facial nerve has not been documented in HCI, but should not be overlooked. Bone deposition in this area is possible as well and facial nerve decompression at this level in would be less dangerous.

Later on in life, symptoms tend to be less predictable, largely depending on the severity and location of the hyperostosis. Several individuals in the family have longstanding facial palsies. Facial nerve function tends not to deteriorate during life. Late facial nerve decompression is not considered because functional improvement is not expected due to neural degeneration. Most often – in older patients – hearing decreases gradually and only rarely suddenly. Hearing aids can be opted for if speech discrimination is adequate.

In case of severe to profound bilateral sensorineural hearing loss conventional acoustic hearing aids will not be sufficient. Two options can be thought of: cochlear implantation and auditory brainstem implantation. Cochlear implantation will most probably not be feasible due to the dysfunctional cochlear nerve at the level of the internal auditory canal, especially in case of longstanding auditory deprivation. However, if the deafness is not longstanding and is (probably) due to the internal auditory canal, decompression can be opted for. If the hearing does not recover and there is cochlear nerve integrity (upon auditory brainstem response or promontory stimulation) cochlear implantation can be performed. This procedure has been performed successfully in a patient with Camurati Engelmann disease²⁶. If the nerve is not functional, an auditory brainstem implant can be considered. However, the risks of

the operation – especially due to the disturbed anatomy of the posterior fossa and the altered cerebrospinal fluid dynamics should be weighted against the benefits of gain of hearing²⁷. Detection of sound or maybe closed set speech recognition are the maximal audiological results, as discussed in chapter 10.

The two previous subparagraphs illustrate the dilemma of treatment timing. Ideally surgical treatment is performed not long after beginning of the symptoms, because of the reversibility of the nerve function. The disadvantage of late internal auditory canal decompression could be a difficult anatomy with the extra risk of labyrinth damage. Moreover problems related to cerebrospinal fluid circulation are more realistic if the operation is performed at later age, when the intracranial volume is limited due to hyperostosis. On the other hand, patients must be prepared for major surgical interventions, especially in the light of the possible complications.

Pain due to trigeminal neuropathy is treated in a similar way as classical trigeminal neuralgia. Carbamazepine, oxcarbazepine, gabapentin and opioids play a role in the medical treatment, which should be tailored in cooperation with an anaesthesiologist/pain specialist. Pain is often replaced by numbness after a period of time. In case of insufficient effect of medical treatment there might be role for radiofrequency thermocoagulation of the gasserian ganglion. This treatment is only an option if the foramen ovale is reasonably patent. If this is not the case, gamma knife radiosurgery could be an option.

Optic nerve integrity monitoring is described in detail in chapter 4. Summarised, we favour surgical decompression of the optic nerve in two circumstances: in the first place in case of (sub)acute vision loss with proven radiographic optic canal encroachment. Furthermore we opt for decompression in case of significant deterioration of neurophysiologic parameters (visual evoked potentials), of course with radiological proof of optic canal narrowing.

The lower cranial nerves are not affected, not even in the most severely affected patients. If there should be dysfunction of cranial nerves IX-XI, an MRI of the posterior should be made to check for Arnold-Chiari malformation. Whether the detected Arnold-Chiari malformation has clinical implications can be investigated by means of functional MRI: 4D-phase contrast imaging^{28,29}. With this technique cerebrospinal fluid dynamics can be visualised. In case of a symptomatic and radiologically confirmed Arnold-Chiari malformation, a foramen magnum decompression should be performed. Disputable is the coincidence of Arnold-Chiari malformation and trigeminal neuralgia. There has been at least one patient with trigeminal neuralgia without significant hyperostosis at the level of the gasserian ganglion or the level of the superior orbital fissure (NV₁) and the neuroforamina (NV₂ and NV₃). In this patient, who was treated in another center, the trigeminal neuralgia resolved after a foramen magnum decompression. She had an Arnold-Chiari malformation with concurrent nausea and

headaches. Before, the patient had been treated medically and with radiofrequency thermocoagulation (for her trigeminal neuralgia), without success.

The association between Arnold-Chiari malformation and trigeminal neuralgia was first suggested by neurosurgeon Walter Dandy³⁰. In 2008, this topic was elaborated by Papanastassiou *et al.* reviewing the 19 cases in literature with this combination treated with foramen magnum decompression³¹. Several mechanisms have been proposed how Chiari malformation can cause trigeminal neuralgia, such as demyelination of the nerve due to stretching of the nerve and vascular compression at the root entry zone of the nerve.

Generalised headache is also observed in patients with severe hyperostosis. Most probably, this is a direct symptom of increased intracranial pressure. Ophthalmologic examination should be performed to rule out papilloedema. A lumbar puncture to evaluate the intradural pressure is absolutely contraindicated because there is a potential risk of cerebellar tonsillar herniation. Intracranial hypertension can be treated with acetazolamide, especially in older patients when the hyperostosis is not likely to progress anymore. In younger patients, a decompressive craniotomy should be performed. If there is a concurrent Arnold-Chiari malformation, it should of course be a foramen magnum decompression. The most extensive description of a series of decompressive craniotomies for increased intracranial pressure due to cranial hyperostosis is published by Du Plessis in 1993³². The paper describes the treatment in patients with sclerosteosis, which – with calvarial bone up to 4 cm thick – has a much more severe course than HCl. The most important advice is that in case of increased intracranial pressure due to extreme hyperostosis decompression should be performed in a staged and downward fashion: first a bifrontal or bifrontotemporal craniotomy, later a posterior fossa decompression. Two cases in which posterior fossa decompression was performed without supratentorial decompression died because of downward migration of the medulla oblongata. It should be noted that this is not expected in HCl because the hyperostosis is less extensive.

Future perspectives

Obviously it is important for patients to unravel the cause and the pathophysiology of any unknown disease, even when there is only one affected family. Because of the effort of the whole team the course of the disease is now better understood and the causal gene region on chromosome 8p21 has been discovered (chapter 8 and addendum). It is however comprehensible that one questions the need of further investigations of a rare disease knowing that this does probably not lead to a new or causal treatment. Critics might weigh expenses of research against the (short-term) benefits. Well, it is the collaboration with the department of Medical Genetics of the University of Antwerp that proves the opposite. We do believe that it is important for

any patient as well as the treating physician to be informed about the nature of a disease. Besides, sometimes it is only because of the discovery of the pathogenesis of rare disorders like HCl that the complex physiology of normal (bone) metabolism is better understood or can it be a key to the development of treatment options. A promising example is the discovery of the exact mechanism of the SOST-related bone dysplasias, causing disorders with generalised excessive bone formation. It is expected that drugs interacting with this mechanism become a cornerstone in the treatment of osteoporosis in the nearby future.

As the clinically oriented research on HCl is now more or less completed, the road is cleared for the focus on genetic and biochemical studies after the discovery of the causal HCl gene on chromosome 8 by the Antwerp group. We hope to stay involved sideways in the ongoing research of this fascinating disorder and to provide clinical feedback whenever necessary. The unpublished data are part of the PhD thesis of colleague Vere Borra and are brought up as addendum in this thesis. Without the clinical research this study could not have been performed. This study is added to the thesis as addendum, ensuring all available information on HCl is provided.

With exome sequencing a mutation was discovered in the *ZIP14* gene (also known as *SLC39A14*), encoding for a transmembrane protein (see addendum). The ZIP14 protein serves as a zinc transporter³³⁻³⁵ and is mostly expressed in liver, pancreas and heart tissue³⁶. Whereas its function in bone metabolism is not yet clarified, ZIP proteins generally promote zinc transport from extracellular fluid or intracellular vesicles into the cytoplasm. ZIP14 is expressed in osteoblasts and preosteocytes, but not in osteoclasts, suggesting the protein plays a role in bone formation rather than bone resorption. In this study it is proven in an in vitro setting that the mutation prevents the transporter protein from expressing at its usual site at the cell membrane. Instead it accumulates in the cytoplasm and in the nucleus, leading to impaired transport of zinc into the cell. A KS483 cell lineage has been used: murine preosteoblastic progenitor cells.

Human and mouse Zip14 are highly conserved. To investigate the phenotype in an animal model, *ZIP14* wildtype mice (*Zip14*^{+/+}) and *ZIP14* knock-out mice (*Zip14*^{-/-}) have been developed. There is an obvious relation of *ZIP14* with bone formation as knocking out the *ZIP14* gene causes growth retardation measured with micro-CT, confirming the results of an earlier conducted study³⁷. However, this genotype has no visible influence on the craniofacial skeleton.

The next phase of the study is a mouse model overexpressing the mutant Zip14 protein (instead of knocking in or out the entire protein) to get more insight in how the identical mutation affects (craniofacial) bone metabolism and subsequent growth.

We hope that gradually we gain more insight in the pathogenesis of the disorder. Eventually there has to be an answer to the riddle why there is only locally disturbed bone metabolism: does the mutant protein bind to another protein, which is specifically expressed in the skull? Is there a relation with the locally expressed

signalling proteins – by the dura mater – involved in growth of the skull? Once the mechanism of this site-specific disturbance is known, the question remains whether this leads to the development of site-specific pharmacological therapy?

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Summary

Hyperostosis cranialis interna is a bone dysplasia which is confined to the skull. There is intracranial hyperostosis and osteosclerosis of the calvaria (skull cap) and the the skull base. The disease has an autosomal dominant inheritance pattern.

To compare the disease to similar bone dysplasias, a review is presented in **Chapter 2**. The ossification of the skull is described in detail, especially the neurocranium, the bone surrounding the brain. As in the rest of the body, in the skull two types of ossification take place: intramembranous ossification is bone formation initiated by mesenchymal stem cells. The calvaria originate largely from intramembranous ossification. Endochondral bone formation is bone formation out of cartilage occurring in different stages. The skull base is largely formed out of endochondral bone formation.

In the review it becomes clear that almost all bone dysplasias display abnormalities throughout the whole skeleton, although predominant involvement of the craniofacial area is common. The disorders can be divided based on metabolic differences: dysplasias with *decreased bone resorption* (e.g. osteopetroses, craniometaphyseal disease, dysosteosclerosis), *increased bone turnover* (e.g. Paget's disease of bone) and *increased bone formation* (e.g. high-bone-mass phenotype, Van Buchem disease, Camurati-Engelmann disease). In the past years many genetic – and hence concurrent molecular – underlying causes of the different diseases have been detected, giving more insight in the pathology and, eventually equally important, different pathways that are essential in bone homeostasis.

In **Chapter 3** the clinical course of HCI is described containing data of 14 patients. Hyperostosis of the skull base causing narrowing of the neuroforamina gives the early symptoms in HCI. Almost all patients present with facial palsy as their first symptom (first or second decade), due to narrowing of the (porus) of the internal auditory canal and entrapment of the facial and vestibulocochlear nerves. Facial palsy is House-Brackmann grade II-IV after an initial temporary complete paralysis. Subclinical hearing loss is often present. Sensorineural hearing loss occurs gradually and is often mild to moderate, but can be severe or profound and also acute. (Bilateral) internal auditory canal decompression is definitely advised in young symptomatic patients, in which skull base anatomy is not grossly distorted.

Anosmia due to hyperostosis of the rima olfactoria is another possible symptom. There is no treatment for this symptom. Neuropathy of the trigeminal nerve should be treated if it presents as neuralgia. Optic neuropathy can occur in severely affected patients and can lead to vision loss, either (sub)acute or slowly progressive.

Symptoms due to decreasing intracranial volume occur later in life and only in severely affected patients. Arnold-Chiari malformation, chronic headache and intracranial hypertension are documented.

In **Chapter 4**, the value of several neurophysiological tests, related to the clinical course of the disorder, is investigated. Ten affected individuals and 13 unaffected family members are tested with visual evoked potentials, masseter reflex, blink reflex, pure tone and speech audiometry, stapedial reflexes, otoacoustic emissions, brainstem evoked response audiometry and electronystagmography.

Apart from tonal and speech audiometry, BERA appears to be very useful to monitor the cochlear nerve function, because a presymptomatic increase of latency time peak I-V is common. (Periodic) vestibular function tests are reliable and of vital importance, because vestibular dysfunction develops gradually and has major clinical impact, especially if present bilaterally. Visual evoked potentials are important to monitor optic nerve function in combination with radiological and ophthalmologic examinations and can be decisive for surgical intervention. We do not advise the routine use of blink and masseter reflex.

In **Chapter 5** the radiologic features of HCI are described. CT scans of affected individuals are analysed and compared to scans of unaffected family members as well as to an age- and sex-matched control group. Linear measurements of the inner table (tabula interna), the diploë (medulla), and the outer table (tabula externa) of different skull locations are performed. Furthermore bone density measurements of the same regions are presented. Neuroforamina widths are recorded as well.

The first radiological abnormalities are subtle: both within the calvaria as well as the skull base small hypodense vesicular islands arise within the medulla. Then focal hyperdense sclerotic spots arise at the border of inner table and the inner diploë, initially without significant thickening of the inner table. Gradually, the hyperdense spots merge, enlarge and form a hyperostotic inner table. In adult patients, there is significant thickening of the skull in the frontal, parietal, temporal, and occipital regions, which is mainly due to thickening of the inner table of the skull. The density of the deposited hyperostotic bone is lower than normal cortical bone.

The width of the porus of the internal auditory canal can decrease to less than 1 mm compared to 4 mm in unaffected individuals. Generally there is extensive pneumatisation of both the paranasal sinuses, as well as the mastoid. Mastoid air cells, however, are gradually replaced by sclerotic bone. Other important radiological landmarks are a sclerotic and enlarged stylomastoid process, unaffected middle and inner ear and subtle mandibular exostoses.

In **Chapter 6** site-specific bone metabolism of patients with HCI was measured using ^{18}F -Fluoride PET/CT. Unaffected family members and unrelated patients were used as controls. Apart from visual assessment of the PET scans, standardised uptake values (SUVs) at different anatomical sites are assessed: frontal bone, sphenoid bone, petrous bone, clivus and control sites. The ^{18}F -fluoride uptake in the entire skull is also measured assessing the uptake in successive axial slides.

It is found that fluoride uptake is statistically significantly higher in the sphenoid bone and clivus regions of patients. No significant differences are seen between the groups concerning the total uptake of the skull. Furthermore, visual assessment confirms CT findings concerning the pathogenesis of calvarial hyperostosis: visually the metabolic activity is located mainly at the transition of the medulla and the base of the hyperostotic border.

This study confirms that ^{18}F -fluoride PET/CT is a very sensitive imaging technique in determining metabolic activity, showing differences in small population sizes, even in conditions with an indolent character. Whereas ^{18}F -fluoride PET/CT is a reliable imaging modality useful in research setting, there is no place for its routine use in HCI patients. Performing this study, ^{18}F -fluoride has been reintroduced as a potentially useful tracer for other bone-related disorders.

Chapter 7 gives an overview of all biochemical bone-related markers that have been assessed in the patients (and non-affected family members): total serum calcium, ionised serum calcium, albumin, parathyroid hormone (PTH) and 25-hydroxy vitamin D were all compared to normative values and no significant differences were found in any marker. C-terminal propeptide of type I collagen (PINP, marker of bone formation) and cross-linked telopeptide of type I collagen (ICTP, marker of bone resorption) were also assessed, but these are more difficult to compare due to age-dependent differences. PINP was found to be relatively lower in affected patients. Furthermore, in chapter 7 histologic images are shown of biopsy specimens of affected bone.

In **Chapter 8** the results of genetic linkage analysis are reported. A genomic search is performed on this family. More than 400 polymorphic markers spread across the genome are analysed. With these results, LOD scores (logarithm of odds) are calculated for each chromosome. Based on the results of the LOD score calculations, genes already known to cause bone dysplasias with involvement of the skull such as *SOST*, *LRP5*, *LRP4*, *ANKH* and *TGFB1* can be excluded as disease causing genes in this family because of LOD scores below -2. One region shows a LOD score of +4.09: a region of 8.3 cM at chromosome 8p21. This region encompasses 4.35 Mb and contains 64 genes. It can be concluded that the gene responsible for HCI is located within this part of the genome. Sequence analysis of three bone-related candidate genes in this region (*BMP1*, *LOXL2* and *ADAM28*) does not show any mutations.

Chapter 9 and 10 are casuistics. Both chapters are about the consequences of internal auditory canal narrowing. In chapter 9 bilateral internal auditory canal decompression via middle fossa approach is described in a child with bilateral short-term facial palsy with good postoperative recovery of facial nerve function. Chapter 10 describes auditory brainstem implantation in a patient with long-term complete bilateral sensorineural hearing loss due to internal auditory canal narrowing. Although

audiologically succeeded, we are faced with an important complication, likely to be caused by the altered cerebrospinal fluid dynamics in a severely hyperostotic skull. These reports underscore that surgical intervention is favoured early in life and that extensive counselling about potential risks is essential.

Chapter 11 comprises the general discussion, conclusions and future perspectives of this research.

Samenvatting

Hyperostosis cranialis interna (HCI) is een botaandoening die zich beperkt tot de schedel. De ziekte kenmerkt zich door intracraniale hyperostose (overmatige botaanmaak) en osteosclerose (bot met een toegenomen botdichtheid) van zowel het schedeldak als de schedelbasis. De aandoening heeft een autosomaal dominant overervingspatroon.

In **Hoofdstuk 2** wordt er een overzicht gepresenteerd om de aandoening te kunnen plaatsen in het scala van vergelijkbare botaandoeningen. Allereerst wordt hierin de ossificatie van de schedel beschreven, met name het neurocranium, het bot rondom de hersenen. Zoals elders in het lichaam kent ook de schedel twee types verbening: intramembraneuze en endochondrale ossificatie. De calvariën (het schedeldak) worden grotendeels intramembraneus gevormd, dat wil zeggen directe botvorming uit mesenchymale stamcellen, vanuit bindweefsel. De schedelbasis wordt grotendeels gevormd door endochondrale botvorming. Hierbij vindt groei plaats vanuit meerdere groeikernen en ontstaat bot vanuit kraakbeen. In de review komt naar voren dat bijna alle botdysplasieën afwijkingen in het gehele skelet vertonen, alhoewel craniofaciale afwijkingen vaak overheersen. Er wordt in de literatuur vaak een metabole classificatie gemaakt van de verschillende aandoeningen: aandoeningen waarbij er sprake is van *verminderde botresorptie* (bv. osteopetroses, craniometaphyseal disease, dysosteosclerosis), *verhoogde botombouw* (bv. Paget's disease of bone) en *toegenomen botaanmaak* (bv. high-bone-mass phenotype, ziekte van Van Buchem, Camurati-Engelmann disease). In de afgelopen jaren is er bij veel ziekten een genetische – en daarmee vaak ook een moleculaire – oorzaak gevonden. Dit heeft bij veel aandoeningen inzicht gegeven in de pathofysiologie. Vaak gaf ook het ontdekken van de pathofysiologie van een bepaalde aandoening nieuwe inzichten in verschillende stappen en cascades van de normale botstofwisseling.

In **Hoofdstuk 3** wordt het klinisch beloop van HCI beschreven aan de hand van data van 14 patiënten. Vroege symptomen van HCI worden doorgaans veroorzaakt door hyperostose van de schedelbasis. Hierdoor treedt er vernauwing op van de verschillende neuroforamina. Bijna alle patiënten presenteren zich initieel met een facialisparese (eerste of tweede decade) ten gevolge van vernauwing van de porus van de meatus acusticus internus (ofwel inwendige gehoorgang) en dus beknelling van de nervus facialis en nervus vestibulocochlearis. Een facialisparese is meestal House-Brackmann graad II tot IV na een tijdelijke volledige paralyse. Ten tijde van de facialisparese is er ook al vaak presymptomatisch gehoorverlies. Perceptief gehoorverlies is langzaam progressief en is doorgaans mild tot matig, maar kan ook ernstig zijn. Acuut gehoorverlies is ook beschreven. (Bilaterale) decompressie van de inwendige gehoorgang is absoluut aangewezen bij jonge symptomatische patiënten, waarbij de anatomie van de schedelbasis nog niet significant verstoord is.

Anosmie ontstaat ten gevolge van hyperostose ter plaatse van de rima olfactoria. Hier bestaat geen behandeling voor. Neuropathie van de nervus trigeminus moet behandeld worden als er sprake is van neuralgie. Neuropathie van de nervus opticus kan optreden bij ernstig aangedane patiënten en kan leiden tot visusverlies, (sub)acuut ofwel langzaam progressief. Symptomen ten gevolge van een verminderd intracranieel volume ontstaan pas later en alleen bij ernstig aangedane patiënten. Er zijn gevallen van Arnold-Chiari malformatie, chronische hoofdpijn en een verhoogde intracranieële druk.

In **Hoofdstuk 4** wordt de waarde van verschillende neurofysiologische tests onderzocht. Bij 10 aangedane en 13 niet-aangedane familieleden werden visual evoked potentials, masseter reflex, blink reflex, toon- en spraakaudiometrie, stapediussreflexen en oto-akoestische emissies, hersenstamaudiometrie (BERA) en elektronystagmografie afgenomen.

Behalve toon- en spraakaudiometrie bleek BERA zeer waardevol voor het monitoren van de functie van de nervus cochlearis. Bij BERA-onderzoek worden vaker verlengde piek I-V latentietijden gevonden voordat patiënten symptomatisch zijn. (Periodieke) vestibulaire functietesten zijn betrouwbaar en zeer belangrijk, aangezien vestibulaire dysfunctie geleidelijk ontstaat. Vestibulaire dysfunctie kan een zeer belangrijke invloed hebben op patiënten, vooral als het bilateraal aanwezig is.

Visual evoked potentials zijn belangrijk voor het opvolgen van de functie van de nervus opticus, in combinatie met radiologisch en oogheelkundig onderzoek. Het resultaat kan doorslaggevend zijn in de besluitvorming omtrent chirurgische decompressie van de zenuw. De resultaten van de blink en de masseter reflex zijn onzes inziens niet consistent en routinegebruik van deze testen is dan ook niet aanbevolen.

In **Hoofdstuk 5** worden de radiologische karakteristieken van HCI beschreven. CT-scans van aangedane individuen worden geanalyseerd en vergeleken met scans van niet-aangedane familieleden en met een controlegroep gematcht op leeftijd en geslacht. De resultaten van lineaire metingen van de tabula interna, de diploë (medulla) en de tabula externa worden getoond. Verder worden er densiteitsmetingen uitgevoerd van dezelfde regio's; ook wordt de breedte van verschillende neuroforamina gemeten en vergeleken.

De eerste radiologische afwijkingen zijn subtiel: zowel ter plaatse van de calvaria als ook de schedelbasis ontstaan er kleine hypodense blazige eilandjes in de medulla. Later ontstaan er focaal hyperdense sclerotische laesies op de grens van de tabula interna met (de binnenzijde van) de medulla. De hyperdense laesies confluëren, vergroten en vormen uiteindelijk een volledig hyperostotische tabula interna die progressief verdikt. Bij volwassen patiënten wordt er een significante verdikking gevonden van het schedelbot in de frontale, pariëtale, temporale en occipitale regio's, voornamelijk ten

gevolge van hyperostose van de tabula interna. Verder wordt er aangetoond dat de densiteit van het pathologisch afgezette bot lager is dan dat van normaal corticaal bot. De porus van de inwendige gehoorgang vernauwt doorgaans tot minder dan 1 mm in vergelijking met circa 4 mm bij gezonde volwassenen. In het algemeen is er bij de patiënten sprake van uitgesproken pneumatisatie van de neusbijholtes en ook het mastoïd. De luchtcellen in het mastoïd maken langzaam plaats voor sclerotisch bot.

Andere belangrijke radiologische kenmerken zijn: een sclerotische en verbrede processus stylo-mastoïdeus, een *niet* aangedaan middenoor en binnenoor en kleine mandibulaire exostoses.

In **Hoofdstuk 6** wordt de mate van botmetabolisme bij patiënten op verschillende gemeten door gebruik te maken van ^{18}F -Fluoride PET/CT. Niet-aangedane familieleden en niet-gerelateerde patiënten worden als controles gebruikt. Behalve visuele beoordeling van de PET-scans wordt de SUV (standardised uptake value) gemeten op verschillende anatomische lokaties: os frontale, os sphenoidale, os petrosum, clivus en controle-plekken. De ^{18}F -fluoride opname in de gehele schedel wordt ook gemeten door de opname in opeenvolgende axiale coupes te bepalen.

Er wordt vastgesteld dat de fluoride uptake significant hoger is bij HCl patiënten in de regio van het os sphenoidale en de clivus. Er werd geen significant verschil gevonden wat betreft de totale ^{18}F -fluoride opname van de schedel. Visuele analyse van de PET/CT scans bevestigt het beeld dat bij de CT-studie werd verkregen over de pathogenese van de hyperostose ter hoogte van de calvaria: de metabole activiteit bevindt zich met name ter hoogte van de overgang van de medulla naar de basis van de hyperostotische tabula interna.

Deze studie bevestigt dat ^{18}F -fluoride PET/CT een zeer gevoelige beeldvormende techniek is wat betreft de bepaling van botmetabole activiteit. Er worden verschillen aangetoond in kleine groepen bij een aandoening met een indolent beloop. ^{18}F -fluoride PET/CT heeft voornamelijk dus een meerwaarde in het kader van wetenschappelijk onderzoek, er is echter geen plaats voor routine ^{18}F -fluoride PET/CT in klinische setting. Deze studie heeft ^{18}F -fluoride opnieuw op de kaart gezet als potentieel nuttige tracer bij dynamisch beeldvormend onderzoek voor andere botgerelateerde aandoeningen.

Hoofdstuk 7 geeft een overzicht van de biochemische botgerelateerde markers die bij de patiënten (en niet-aangedane familieleden) bepaald zijn: totaal serum calcium, geïoniseerd serum calcium, albumine, parathyroïd hormoon (PTH) en 25-hydroxyvitamine D. Alle waarden zijn vergeleken met normatieven en er worden geen significante verschillen gevonden. C-terminal propeptide van type I collagen (PINP, botvormingsmarker) en cross-linked telopeptide van type I collagen (ICTP, botresorptiemarker) zijn ook gemeten, maar onderlinge vergelijking is moeilijker in verband met de leeftijdsgebonden verschillen in de waarden. PINP was relatief lager in de aangedane individuen. Verder worden er in dit hoofdstuk afbeeldingen getoond van histologische coupes van aangedaan bot.

In **Hoofdstuk 8** worden de resultaten van de genetische koppelingsanalyse getoond. Er is een genoomstudie werd verricht bij de familie. Meer dan 400 polymorfe merkers verspreid over het hele genoom zijn geanalyseerd. Met de resultaten zijn LOD-scores (logarithm of odds) berekend voor elk chromosoom. Op basis van de resultaten van de LOD-scores (< -2) zijn bepaalde genen met belangrijke betrokkenheid bij botstofwisseling worden uitgesloten van betrokkenheid bij HCI: *SOST*, *LRP5*, *LRP4*, *ANKH* en *TGFB1*. Eén regio toont een LOD-score van +4.09: een regio van 8.3 cM op chromosoom 8p21. Deze regio bevat 4.35 Mb met daarin 64 genen. Er wordt geconcludeerd dat het gen dat verantwoordelijk is voor HCI zich bevindt in dit gebied van het genoom. Sequentieanalyse van drie botgerelateerde kandidaatgenen in deze regio (*BMP1*, *LOXL2* en *ADAM28*) tonen geen mutaties.

Hoofdstuk 9 en 10 bevatten casuïstiek. Beide hoofdstukken hebben te maken met de gevolgen van vernauwing van de inwendige gehoorgang. In hoofdstuk 9 wordt de bilaterale decompressie van de inwendige gehoorgang beschreven bij een kind met (relatief) kortstondige bilaterale facialisparese met goed post-operatief resultaat. Hoofdstuk 10 gaat over het plaatsen van een “auditory brainstem implantaat” bij een patiënt met langdurige bilaterale volledige doofheid. Hoewel de ingreep een audiologisch succes is, treedt er een belangrijke complicatie op, mogelijkterwijs deels ten gevolge van de veranderde liquorcirculatie in de ernstig hyperostotische schedel. Deze casus onderstrepen het belang van vroege chirurgische interventie, indien mogelijk, en ook het belang van uitgebreide inlichting van patiënten over de risico's van dergelijke ingrepen.

Hoofdstuk 11 is een algemene beschouwing. Ook worden de conclusies van het onderzoek genoemd en worden de toekomstperspectieven van het onderzoek geschetst.

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Curriculum Vitae

Jérôme Joseph Waterval was born on May 10th 1982 in Heerlen, The Netherlands. He did classical studies (gymnasium) at the Bernardinuscollege in Heerlen and started his medical studies at the University of Maastricht in 2000. As a medical student he did several electives abroad (Bangkok, Brisbane and Trinidad & Tobago), his passion for travelling being born. Shortly after finishing medical school in 2006 he worked as a resident in the field of neurosurgery during five months (Maastricht University Medical Centre), however the fascination for otorhinolaryngology, his last elective, did not get out of his mind. In 2007 he enrolled in his otorhinolaryngology training with great enthusiasm in the same hospital, with prof. dr. Bernd Kremer and prof. dr. Robert Stokroos as his supervisors. At the same time he started this PhD project. Part of the training consisted of working at the Catharina Hospital in Eindhoven (under supervision of dr. Frank Adriaansen, dr. Nies Mateijsen and dr. Maarten Tabor) and at the Elkerliek Hospital in Helmond (under supervision of dr. Paul Schuil, drs. Harm Kahmann and drs. Martijn Alles). Before finishing his general training he spent two months as a medical observer at the Royal Victorian Eye & Ear Hospital in Melbourne with prof. Stephen O'Leary and assoc. prof. Robert Briggs. The otologic group in this hospital have had a pioneering role ever since the development of the first cochlear implants. Furthermore, at the end of the last year of his training he joined Eardrop for a medical mission in Ethiopia. In September 2012 he started a fellowship in otology & neurotology at the European Institute for Otorhinolaryngology headed by prof. dr. Erwin Offeciers and dr. Thomas Somers (Wilrijk – Antwerp), where he was given the chance to participate in one of the leading European otologic groups. In February 2014 he started working at the Academic Medical Centre in Amsterdam as staff member otology with dr. Fenna Ebbens, drs. Erik van Spronsen and prof. dr. Bert van der Baan at the department led by prof. dr. Wytske Fokkens.

He lives together with his partner Stephanie Bukkems and their son Florian.

