BRAIN IMAGING IN MILD TRAUMATIC BRAIN INJURY AND NEUROPSYCHIATRIC DISORDERS: A QUANTITATIVE MRI STUDY

The studies presented in this thesis were performed at the Department of Radiology and the Department of Neuropsychology and Psychiatry of the Maastricht University. Both departments participate in the the Maastricht Brain & Behaviour Institute.

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PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht op gezag van de Rector Magnificus, Prof. Dr. A.C. Nieuwenhuijzen Kruseman volgens het besluit van het College van Decanen in het openbaar te verdedigen op donderdag 18 mei 2000 om 16.00 uur

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Dit proefschrift draag ik op aan
mijn ouders, Ingrid en Zelie

List of abbreviations

AD	Alzheimer's disease
ADP	alcohol dependent patients
CI	confidence interval
CIND	cognitive decline no dementia
CNS	central nervous system
CSF	cerebrospinal fluid
CST	concept shifting test
CT	computed tomography
DAI	diffuse axonal injury
DSM	diagnostic and statistical manual of mental disorders
ETL	echo train length
FFE	fast field echo
FLAIR	fluid attenuated inversion recovery
FPR	false positive rate
GCS	Glasgow Coma Scale
Tc99m-HMPAO	technetium 99m hexamethylpropylamine-oxime
HRSD	Hamilton rating scale for depression
ICH	intracranial haemorrhage
KS	Korsakoff's syndrome
LOC	loss of consciousness
LDST	letter digit substitution test
MCRT	motor choice reaction test
MR	magnetic resonance
MRI	magnetic resonance imaging
MT	magnetisation transfer
mTBI	mild traumatic brain injury
MTC	magnetisation transfer contrast
MTI	magnetisation transfer imaging
MTR	magnetisation transfer ratio
NPV	negative predictive value
NSA	number of signal averages
PCS	post-concussional syndrome
PPV	positive predictive value
PTA	post-traumatic amnesia
PVH	periventricular hyperintensity
ROC	receiver-operator characteristic
ROI	region of interest
SCH	subcortical hyperintensity
SCWT	Stroop colour word test
SPECT	single-photon emission computed tomography
TE	echo time
TI	repetition time
TPR	true positive value
VBR	ventricle brain ratio
VRS	Virchow-Robin space
VVLT	visual verbal learning test
WMH	white matter hyperintensity

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- CHAPTER 1 -

GENERAL INTRODUCTION

Introduction

In 1761, a French officer of ‘great rank and merit’, Count de Lordat overturned his carriage on the way to his regiment. ‘His head was pitched against the top of the coach; his neck was twisted from left to right; his left shoulder, arm and hand were much bruised’. After the accident he walked to the next village, and continued his journey. He went through the fatigues of the campaign, but six months after the accident he developed dysarthria and a left hemiparesis. He was able to undertake another campaign with his regiment, but ultimately his impairments forced him to leave the army. Four years after the accident the Count died, and the post-mortem examination showed a pia mater said to be full of blood and lymph and the medulla oblongata was greatly enlarged. It was concluded his condition was related to the accident four years before[1].

The above description is an early example of a seemingly trivial accident that may lead to a neurologic deficit. This and other observations led Erichsen in 1882 to the publication of "On the concussion of the spine, nervous shock, and other obscure injuries to the nervous system in their medicolegal aspects". Although Erichsen suggested that accidents leading to these injuries occur in daily life, he stated that railway accidents are the most frequent cause of spinal concussion. He proposed that patients suffering from post-traumatic symptoms have microscopic alterations of their central nervous system. A few years later Page published a book which was essentially a rebuttal of the ideas expressed by Erichsen [2]. He stated that those complaining from post-traumatic symptoms without signs of mechanical lesions suffer from a post-traumatic neurosis, and that their symptoms are psychological in origin. On the other hand, in 1889 Oppenheim postulated that ‘molecular disturbance of neuronal function’ to be the cause of post-traumatic neurosis [3], and that the term ‘railway brain’ was more appropriate than ‘railway spine’, since the brain was the seat of many of the conditions. An increasing knowledge of the effects of trauma on the brain has led to the understanding that changes in patients’ behaviour can be attributed to brain lesions. The classical example is that of Phineas Gage, a construction worker who was struck by an iron rod, which entered his head just below the left eye and left through the top of his head. Mr. Gage recovered and appeared normal, except for his drastically and permanently changed personality [4].

The problem: are neuropsychiatric conditions characterized by brain lesions

It is nowadays recognized that behavioural disorders, personality changes and problems in the planning, programming and evaluation of behaviour can be the direct consequence of brain lesions. Many different causes are known, varying from traumatic origin through neurodegenerative to cerebrovascular conditions. Especially prefrontal regions seem to be involved in these conditions[5-8]. In the past decade, knowledge has accumulated that not only behavioural and neurocognitive changes could be the direct result of a lesion in the brain and especially in the prefrontal lobes, but that psychiatric conditions could also be the consequence of a traumatic or degenerative brain lesion. For example, cerebrovascular lesions in the frontal lobe may give rise to mood disorders. The nature of the mood disorder, whether it is depressive or manic in nature, depends on the location of the lesion [9-11].

However, as in the 19th century, for many psychiatric disorders the debate on the possible organic aetiology is still ongoing**.** Although the strict separation between psychogenic and organic aetiology of neurocognitive and neuropsychiatric disorders no longer exists, organic lesions still provide legitimacy to neurocognitive and neuropsychiatric disorders. It is of importance for patients and for health care professionals to evaluate whether an organic lesion could be present, because it would enable them to attribute the problems to both biological and non-biological factors; it would dismiss the prejudice that the patient's condition would be due solely to environmental or psychological causes. Showing cerebral changes in patients with a psychiatric or neuropsychiatric condition has a considerable impact. This is because it may give a clue for aetiological factors involved and for the relative contribution of biological and non-biological factors. A better understanding can ultimately lead to improvements in treatment or care. The present thesis has as therefore as its aim to increase our understanding of possible organic factors in the aetiology of neuropsychiatric conditions.

The approach: magnetic resonance imaging in neuropsychiatric conditions

In this thesis two patient populations will be studied: firstly subjects who suffered a mild traumatic brain injury, and secondly patients with neuropsychiatric conditions. For both groups there is an ongoing debate on the organicity of the psychiatric and neurocognitive symptoms

and signs. The research which was performed in this thesis makes mainly use of magnetic resonance imaging (MRI) in these two patient populations. It was the aim to evaluate the possible presence of cerebral changes using neuroimaging techniques. This is because MRI is currently the most sensitive, non-invasive technique that allows for the visualisation of brain parenchyma. MRI enables the distinction of normal and diseased tissue as well as structural assessment of the brain. Because of the non-invasive nature of MRI this technique is suitable to study a large number of patients and healthy individuals. Previous studies have shown MRI to be sensitive to cerebral differences between normal subjects and patients with psychiatric disorders. For example, in schizophrenia research Andreasen et al performed innovative investigation using MRI[12-15]. Recently Anderson et al showed that prefrontal lesions acquired in early childhood may lead to impaired social behaviour, they also used MRI to assess these cerebral changes[16]. Furthermore, MRI is a fast evolving technology, and many new techniques have been introduced. Assessment of these new techniques and a quantitative approach to more ‘conventional techniques is needed to evaluate the value of brain MRI in the neuropsychiatric disorders.

Two types of minimal brain lesions are studied: those that are due to mild traumatic brain injury, and those that resemble brain alterations that are associated with the process of normal aging.

Brain changes due to mild traumatic brain injury

The first type of brain lesions that are studied are caused by mild traumatic brain injury. For many decades it has been a popular belief that mild traumatic brain injury does not cause brain damage, and many health care professionals still share this view. However, traumatic brain injury is now considered the most common cause of neurocognitive dysfunction in young individuals. Six months after a mild traumatic brain injury 15-29% of the patients still appear to have appreciable complaints[17]. With an increasing demand on subjects, even a minor neurocognitive deficit may pose a significant problem. Especially reduction in the speed of information processing, and problems with shifting attention may hamper a subject in daily life[18, 19]. Mild traumatic brain injury is a common condition: in the Netherlands the estimated incidence of head injury is between 20.000 and 100.000 per year. Most of these patients (80 to 90%) sustain a mild traumatic brain injury. However, little is known about mild traumatic brain injury, the prevalence of brain lesions and their precise nature is unknown and the association between brain lesions and persistent neurocognitive deficits has not been

studied. So far most studies on head injury have focused on moderate and severe head injury. Thus, there is a need for new studies into the involvement of brain lesions in mild traumatic brain trauma and the correlation of these lesions with neurocognitive complaints. This is what the studies in this thesis aim at.

White matter changes

The second category of lesions have been referred to as leucoaraiosis[20], unidentified bright objects (UBO's), and white matter hyperintensities (WMH). With the introduction of computed tomography (CT) leucoaraiosis was found in healthy subjects[21], and in patients with neuropsychiatric disorders[22, 23]. Recently, a large population study in healthy subjects aged 60-90 showed that the severity of white matter lesions was directly proportional to deterioration in neurocognitive performance and in depressive symptomatology[24]**.** The superior sensitivity of MRI in detection of brain lesions and its lack of adverse effects has led to several publications on minimal brain lesions. However, these studies presented conflicting results with regard to prevalence of minimal brain lesions and to the association between these lesions and neurocognitive and neuropsychiatric disorders. These different results may be due to differences in scanning, rating method and population selection. Thus, there is compelling evidence to suggest that it is of importance to study WMH in neuropsychiatric conditions. This is what the studies in the present thesis aim at**.**

Research questions and outline of the thesis

In chapter two an overview is given of the types of brain injury, and the application of neuroradiological methods in the clinical management of mild traumatic brain injury. The place of computed tomography, magnetic resonance imaging and single-photon emission tomography is briefly discussed.

Because the skull X-ray is still widely used in Europe in the initial management of mild traumatic brain injury patients the value of this technique is assessed in a meta-analysis in chapter three.

Magnetic resonance imaging is very sensitive to cerebral lesions, and this technique is widely applied in population studies in healthy subject and subjects with neuropsychiatric disorders. However, not all acquisition techniques are equally sensitive and certain pulse

sequences are especially sensitive for detecting white matter changes. In chapter four such a technique is explored. This technique, magnetisation transfer imaging, allows for global quantitative assessment of cerebral parenchyma, and therefore this technique can be useful in population studies. First a post-processing technique is introduced that allows quantitative assessment of white matter. In order to gain understanding of the effects of age and sex on the cerebral white matter this technique is used to describe white matter changes in normal aging and to study differences between males and females.

The next two chapters deal with radiological evaluation of the consequences of mild traumatic brain injury. Previous studies have shown that many patients suffer from persisting neurocognitive complains after a seemingly trivial head injury. Although it seems plausible that there is an association between neurocognitive symptoms or complaints and cerebral lesions, this association has never been studied. In chapter five a group of patients who developed a persisting post-concussional syndrome after mild or moderate brain injury is studied and the results of brain imaging are compared with those from healthy subjects.

Retrospective studies have the potential for a selection bias. This is less of a problem in prospective longitudinal studies. Chapter six presents therefore such a study of mild traumatic brain injury patients. Patients were assessed with MRI and perfusion single photon emission tomography (SPECT) in the subacute phase and MRI was repeated after six months. The aim of this study was to assess the correlation between traumatic brain lesions and neurocognitive changes.

Chapter seven to thirteen deal with the association between white matter hyperintensities (WMH) and neuropsychiatric disorders. Chapter seven is a introduction to the subject in which a few methodological issues are discussed.

In order to be able to interpret the association between WMH and neuropsychiatric disorders it is mandatory to study the relation between WMH and age, this is described in chapter eight. Chapter nine describes the association of WMH with schizophrenia. Chapter ten describes the association of WMH with bipolar mood disorders, and chapter eleven describes the association with Alzheimers's disease. Chapter twelve reports the association with cognitive decline, and chapter thirteen describes the association with alcohol-related disorders. A general discussion of white matter hyperintensities in neuropsychiatric disorders is given in chapter fourteen. Chapter fifteen are the concluding remarks, in which an evaluation is given over the approach used in this thesis, and the implications for future research and possible clinical applications.

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- CHAPTER 2 -

BRAIN LESIONS IN MILD TRAUMATIC BRAIN INJURY; PATHOPHYSIOLOGY AND IMAGING

Introduction

Head injury is one of the most common neurologic disorders, with only migraine and herpes zoster having a higher incidence[1]. In the western world it is one of the leading causes of disability in the young population[2]. Closed head injury is commonly divided into three severity grades; mild, moderate and severe. Although only a minority of head injuries is moderate or severe, most research effort has been put into these two categories. These patients suffer the most serious injury and need clinical attention in the acute phase. Treatment is guided by understanding of the pathophysiology of head injury and the results of brain imaging and clinical assessment. The majority of patients (80 to 90%) sustain a mild traumatic brain injury (mTBI) and do not need hospitalization or sophisticated health care. If these patients attend the emergency department of a hospital, almost all are sent home. This does not mean that mTBI is an innocuous event. Although the majority of patients recover without medical intervention, some develop acute life-threatening complications such as an epidural haematoma[3, 4]. In a retrospective study of 610 mTBI patients, 3% required a neurosurgical procedure[5]. In addition, 15-29% of mTBI patients have post-traumatic complaints persisting after six months[3]. Beyond this point there is only a slight further decline in morbidity. This chapter provides an overview of the mechanisms of brain injury and the contribution that neuroimaging can make in the assessment and management of these mTBI patients.

There is no consensus on the definition of mild traumatic brain injury, although most authors use the Glasgow Coma Scale (GCS) to assess severity of trauma[6]. The classification of patients into three categories of mild, moderate and severe is primarily based on clinical data, although some authors use the findings of computed tomography (CT) as well. There is a wide range of definitions, but there appears to be a consensus in favour of criteria along the lines developed by The Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine[7], which considers mild traumatic brain injury to have occurred when the period of unconsciousness is less than 30 minutes, GCS score on admission is 13-15 and has never fallen below 13, and the neurological examination may show (transient) focal deficits normal. Post-traumatic amnesia does not exceed 24 hours.

Types of brain injury

Brain trauma is a complex process with multiple factors including the type and severity of injury, the physiological reactions following the injury which may lead to secondary injury. This overview will be limited to the effects of non-perforating mechanically induced head trauma or closed head injury. The reader is referred to[8-11] for a more in depth description.

Usually three types of traumatic brain lesions are usually distinguished: coup lesion, contrecoup lesion and diffuse axonal injury (DAI). These are described in the next paragraphs, as well as extra-cerebral haemorrhages. One clinical syndrome, that is concussion, does not fit in this classification and is described separately.

Coup lesion

The coup lesion is located at the point of impact on the skull. If the skull is fractured the lesion is referred to as a fracture contusion. The lesion to the cerebral parenchyma is caused by direct disruption of tissue due to the mechanical force or to negative pressure in the brain parenchyma that may occur if the skull moves back to it original position[12]. Focal damage to the brain surface, with or without haemorrhage, but with intact pia-arachnoid is called a contusion. Macroscopically the lesion is characterized by multiple punctate haemorrhages, and microscopic neural and axonal damage is found. The injury results in oedema which may increase intracranial pressure and give rise to secondary brain injury. When the pia-arachnoid is ruptured and there is extensive damage to the underlying brain the lesion is described as a laceration[13].

Contrecoup lesion

The mechanism of the contrecoup lesion is less straightforward. A contrecoup lesion is located opposite the site of impact. The classical example of a coup-contrecoup lesion is a fall on the occiput, in which the occipital coup lesion is small or absent and a frontal contrecoup lesion is relatively large. Since the brain is loosely suspended in the skull vault by the falx and tentorium, and surrounded by CSF, the brain lags behind when the head is suddenly accelerated or decelerated, and the brain may therefore be thrust against the opposite calvarium, falx, tentorium or skull base[8]. This mechanism can explain the contrecoup phenomena in some cases. The microcavitation theory gives a different explanation for the contrecoup mechanism. Experimental studies have demonstrated that at the site of impact there is an increased pressure, and a negative pressure gradient towards the site opposite to that of impact. At a certain point the pressure becomes negative, and brain parenchyma appears to be more easily damages by

an abrupt negative pressure than to a positive pressure. The negative pressure causes formation of microscopic gas bubbles that disrupt brain tissue[8, 14].

A third possible explanation is the positive pressure gradient within the brain. When the brain lags behind during acceleration, the brain at the impending impact site experiences a negative acceleration pressure, whereas the brain at the opposite site experiences a positive acceleration pressure. The negative acceleration pressure at the coup site protects the brain from the positive pressure of the impact. The pressure wave passes through the brain and at the contrecoup site this pressure wave augments the still existing positive acceleration pressure, resulting in more severe injury[8, 15]. Which theory best explains the formation of a contrecoup lesion may depend on injury type. It appears that the brain lag is essential in the formation of a contrecoup lesion. This explains why contrecoup contusions are very rare in injuries where the head was fixed.

Diffuse axonal injury

The third type of injury is diffuse shearing or diffuse axonal injury (DAI). The direct impact of a trauma causes contusion and a laceration, but indirect forces that cause no skull deformation may produce a shearing injury of the brain tissue at the interface of tissues with a different stiffness. Holbourn developed this theory using a gelatine model of the brain. He proposed a model with a changing shape of the brain without a change in the volume resulting in shear-strain injuries[16, 17]. This work was further elaborated on by Strich[18, 19]. Gennarelli and Adams proposed the term diffuse axonal injury and demonstrated in vivo the effect of acceleration-deceleration trauma[20, 21].

Rotational forces are especially likely to cause shearing injury to the white matter. With increasing energy first the lobar white matter is affected, then the corpus callosum is damaged, followed by the dorsolateral quadrant of the mesencephalon[13, 20, 22]. Not only severe head injury but also minor trauma may cause axonal disruption with or without associated vascular damage[19, 20, 23]. In mTBI the lobar white matter is the most important location of DAI.

Based on the mechanisms described above Gean distinguishes four basic types of head trauma[8].

1. Moving head against stationary object -> coup lesion (small) contrecoup (large)
2. Moving object against fixed head -> coup lesion
3. Non-fixed head against moving object -> coup lesion with possible DAI and contrecoup lesion
4. Deceleration without local impact -> DAI

Because of the oval shape of the head and the eccentric position of the cervical spine, lateral impact gives a more rotational movement and results in DAI whereas impact on the AP axis gives rise to a coup and contrecoup lesion.

Extracerebral haemorrhage

Traumatic haemorrhage results from injury to a cerebral vessel. Subdural haemorrhage is caused by disruption of cortical veins due to differential movements of the brain and adherent cortical veins with respect to the skull and attached sinus (shearing injury)[11]. The bridging cortical veins are most vulnerable. The majority of patients with acute subdural haemorrhages have severe parenchymal brain lesions as well[13]. The occurrence of epidural haemorrhage is typically associated with a skull fracture and rupture of a meningeal artery (90%) or venous sinus (10%). Sub- and epidural haemorrhages each have a distinctive radiological appearance. The classic appearance of an acute epidural haematoma is a well-defined biconvex-shaped extra-cerebral mass causing compression of the brain. An acute subdural haematoma presents as a crescent-shaped extra-cerebral collection that spreads diffusely over the hemisphere, and is often associated with extensive contusion and swelling of the brain. Both types of haemorrhage are occasionally found in mTBI patients.

Concussion

The definition of concussion is a temporary dysfunction of the brain, as a result of a blow or impact. The clinical signs are loss of consciousness lasting less than 20 minutes and subsequently a GCS score of 13 or higher, returning to a normal score of 15 within 48 hours. Patients have no focal neurological deficits. This definition resembles the definition of mTBI. The major site of physiological impairment is likely to be the brain stem[24], which could explain the temporary loss of consciousness in these patients. Evidence for brain lesions in concussion come from animal studies which have shown patho-anatomical changes after minor head injury including mitochondrial swelling, oedema and axonal disruption[25, 26]. In humans mTBI may also result in damage to neural structures. This has been shown in patients who died of a non-CNS related injury shortly after a minor head trauma[27], and recent imaging studies have shown lesions in mTBI patients[28, 29]. Because concussion implies a mild injury without brain damage, the term is misleading and should not be used.

The biomechanics of closed head injury is complex. Head position, support and fixation, as well as the magnitude of the force and the site and direction of impact all determine the ultimate damage. In mTBI patients all types of lesions may be found. The frontal lobe, temporal pole, and limbic system are most vulnerable in brain injury [30]. It is interesting to note that many of the persistent neuropsychiatric symptoms can be grouped as frontal lobe syndromes, and these may be caused by damage to the frontal neuronal circuits.

Brain Imaging

Introduction

brain imaging of patients who have suffered mild traumatic brain injury serves two goals. The primary goal is to assess the severity of the injury to the brain in order to direct to management of patients (e.g. neurosurgical intervention). A second objective of imaging can the assessment of the prognosis with regard to the risk of persistent symptoms. This second objective, however, is not yet an issue in clinical practice, since the relation between visible brain damage and neurocognitive outcome is still a matter of research. Plain skull X-rays and computed tomography (CT) are used most in imaging mTBI patients. Magnetic resonance imaging (MRI) has proven to be more sensitive to cerebral injury than CT, but the additional value of MRI has to be determined. In principle functional imaging techniques such as perfusion single-photon emission computed tomography (SPECT) and functional MRI might provide more insight in the pathophysiological processes involved in post-concussional sequelae.

Plain skull X-ray

Before the introduction of CT and MRI the majority of head injury patients were imaged only with a plain skull X-ray . Even at this moment the plain skull X-ray is used in initial assessment of many mTBI patients. However, this technique does not provide information on brain parenchyma, but only on the skull, and there is little correlation between skull and intracranial injuries. Therefore the value of plain skull X-ray in the assessment of mTBI is of little value. In chapter 3 a meta-analysis is presented that gives a more thoroughly coverage of this issue.

Computed tomography

The introduction of CT in 1972 by Hounsfield has revolutionized the management of head injury patients31, 32. It has become the modality of choice to study acute head injury patients. It has replaced cerebral angiography for the detection of intracranial mass lesions and cerebral herniation. The majority of acute traumatic intracranial lesions can be adequately assessed by CT without the use of intravenous contrast agents. The main goal of imaging is to detect lesions that require neurosurgical intervention, and CT is sufficiently sensitive for this purpose. In mTBI the reported prevalence of intracranial haemorrhage detected by CT ranges from 0.034 to 0.1833.

Magnetic resonance imaging

The initial imaging in closed head injury patients should be tailored to the clinical condition. In practice this means that mTBI patients will undergo no imaging in the majority of cases. MRI is not routinely applied in this category. MRI however, is significantly more sensitive than CT for a broad range of post-traumatic injuries[34]. In a comparative study the overall sensitivity of MRI for the detection of lesions in acute head injury was 96.4%, compared to 63.4% for CT. For extra-cerebral haematomas the sensitivity of MRI and CT were 97% and 31%, respectively. A standard-of-reference diagnosis for each patient was based on the complete patient information, including follow-up examinations. The only lesions for which CT had a higher sensitively were fractures[34]. This superior sensitivity of MRI for post-traumatic injury has also been shown in other studies[35, 36].

MRI has been applied in patients with mTBI, and Jenkins et al[37] were among the first to show that MRI is more sensitive to post-traumatic changes than CT. In eight mTBI patients they found six patients with cortical lesions, whereas CT detected approximately half of the lesions. Yokota found 97 lesions with MRI in 134 mTBI patients, CT found only 62 of these lesions[36], and MRI revealed abnormalities in 62% of patients whereas CT detected lesions in 45% of patients.

Another group with mTBI is described by Doezema et al[29]. Fifty-eight selected mTBI patients were imaged with a low-field MRI system within 24 hours after injury. All CT studies performed were negative, and none of the patients had been admitted to hospital. Of this group six patients (10%) had an abnormal MRI study. Mittl et al[28] found a much higher prevalence of post-traumatic changes in a similarly defined population. They found signs of diffuse axonal injury in 30% of patients. This difference can be explained by the higher field strengths applied (1.5 Tesla versus 0.064 Tesla) and the pulse sequence used. Mittl et al used a gradient-echo T2*-weighted sequence instead of a spin-echo sequence to assess small haemorrhagic lesions associated with diffuse axonal injuries.

New scan techniques can enhance the sensitivity of MRI further. Magnetisation transfer imaging is a relatively new technique shown to be sensitive to post-traumatic white matter changes[38, 39]. Especially in the subacute and chronic phase this technique will likely prove to be of value in the assessment of post-traumatic damage. Fluid attenuated inversion recovery (FLAIR) sequences have a higher sensitivity than spin-echo sequences, not only for parenchymal lesions[40], but also for the detection of subarachnoid haemorrhage[41, 42]. The use of gadolinium DTPA does not increase the sensitivity in the acute phase, as lesions enhance only after 96 hours post-trauma[43]. Barzo et al[44] showed that in the acute phase after trauma the blood-brain barrier is temporary disrupted throughout the entire brain. Within minutes the blood-brain barrier regains its integrity. However, in those subject with hypotension and hypoxia the blood-brain barrier remains disturbed longer and to a greater extent. Ito et al[45] used diffusion

weighted techniques to differentiate primary from secondary brain damage. These two techniques have been developed in animal studies and to our knowledge not been applied in humans. However, if these techniques were to show secondary injury in mTBI, this would have significant impact on the management of mTBI patients. Little is known about the additional value of MR spectroscopy in neurotrauma. Functional MRI may be of use in the evaluation of rehabilitation potential of head injury patients, but further study is needed.

Single-photon emission computed tomography

Single-photon emission computed tomography (SPECT) studies can detect abnormalities of cerebral blood flow indicating areas of dysfunction secondary to cerebral trauma. SPECT has proved to be more sensitive than CT for the detection of post-traumatic lesions. Nedd et al[46] described a prospective series of 16 trauma patients, who all had CT and SPECT of the brain. Thirteen of these patients suffered mTBI. CT detected abnormalities in six patients, whereas the SPECT study was abnormal in 14 patients. The SPECT studies were performed between 1 and 9 days after the trauma, and the time from injury to CT ranged from 0 to 7 days. Masdeu et al[47] studied 14 mTBI patients with brain SPECT performed within 48 hours of trauma. All patients had a normal CT, and SPECT studies were abnormal in 10 patients. Focal cortical lesions were found as well as diffuse areas of hypoperfusion. Roper et al[48] found that 39% of lesions seen on SPECT were not seen on CT, and that 27% of the abnormalities seen on CT were not seen on SPECT. That cerebral perfusion is unchanged in some lesions can be explained by luxury perfusion due to uncoupling of flow and metabolism. No studies are available on the correlation of acute or subacute brain SPECT and MRI in head injury patients.

SPECT imaging in the chronic phase may predict ultimate outcome. Jacobs et al[49] found that a normal SPECT study predicts a favourable clinical outcome. In a highly selected group of 14 subject with persisting neurocognitive complaints, Varney et al[50] found reduced perfusion in the anterior mesial temporal lobe. These patients all had normal CT and MRI studies. In another study of patients with a persistent post-concussional syndrome, 53% was characterized by abnormal SPECT findings, whereas only 8% showed abnormalities on MRI[51]. Moreover there was limited concordance between the two neuroimaging techniques. Similar findings were published by Ichise et al[52].

SPECT imaging provides information complementary to morphological images provided by CT and MRI. However, the characterization of an area of asymmetric activity on a SPECT image as a lesion requires a more fundamental knowledge of the relationship between brain pathology and SPECT images. There is a complex association of various factors involved in patients' mental or psychological status, and brain perfusion. The additional value of SPECT in the chronic phase after a head trauma remains controversial; while it is not surprising that a

functional imaging technique reveals abnormalities in subject with neurocognitive complaints, the causal relation however is unclear.

Conclusion

Mild traumatic brain injury patients have the same type of lesions as moderate and severe head injury patients, only to a lesser extent. The prevalence of intracranial haemorrhage after mTBI is approximately 0.083, as diagnosed by CT[33]. MRI has a higher sensitivity to post-traumatic lesions and will reveal significantly more lesions. Therefore the true prevalence of post-traumatic lesions after mTBI is probably much higher. At this moment the superior sensitivity of MRI does not lead to a change in management of patients, and CT fulfils the needs of the clinician. Brain perfusion studies have shown to be sensitive to post-traumatic changes as well, and subjects with a persistent post-concussional syndrome often show more abnormalities on SPECT studies, without lesions on MRI or CT. MRI and SPECT can be of value in the assessment of the full extent of post-traumatic damage. This is one of the factors influencing final outcome, and knowledge of these lesions can direct future research and treatment.

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- *CHAPTER 3* -

VALUE OF RADIOLOGICAL DIAGNOSIS OF SKULL FRACTURE IN THE MANAGEMENT OF MILD TRAUMATIC BRAIN INJURY: A META-ANALYSIS

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Abstract

Objectives-Head injury is a common event. Most patients sustain a mild traumatic brain injury (mTBI), and management depends on the risk of an intracranial haemorrhage (ICH). The value of a plain skull X-ray as screening tool for ICH is controversial. The aim of this meta-analysis is to estimate and explain differences in reported sensitivity and specificity of the finding of a skull fracture for the diagnosis of ICH, in order to assess the value of the plain skull X-ray in the work-up of mTBI patients, and to estimate the prevalence of ICH in these patients.

Method-After a systematic literature search 20 studies were selected that reported data on the prevalence of ICH after mTBI and/or data on the diagnostic value of skull fracture for the diagnosis ICH. The mean prevalence of ICH weighted for the sample size was determined. The sensitivity and specificity of different studies were combined using a summary receiver operator characteristic curve. Correlation analysis was used to determine factors that could explain the reported differences between studies.

Results-The weighted mean prevalence of ICH after mTBI is 0.083. The potential for verification bias and the percentage of patients who had suffered loss of consciousness or post-traumatic amnesia were the most significant factors explaining inter-study differences in sensitivity and specificity. Based on studies wherein at least 50% of patients had a computed tomography study of the brain, the estimated sensitivity of an X-ray finding of skull fracture for the diagnosis of ICH is 0.38 with a corresponding specificity of 0.95.

Conclusion-The plain skull X-ray is of little value in the initial assessment of mTBI patients.

Introduction

Head injury is one of the most common injuries and can be considered a silent epidemic. In the Western world it is one of the leading causes of disability, especially in the young population. The Head Injury Task Force of the National Institute of Neurologic Disorders has estimated that there are 2,000,000 cases of head injury in the USA annually. In The Netherlands the estimated incidence of head injury is 0.14- 0.64%[Twijnstra 1998, personal communication], slightly less than the reported incidence in the USA. Most patients (80% to 90%) sustain a mild traumatic brain injury (mTBI) and do not need hospitalization or sophisticated health care. If these patients attend the emergency department of a hospital, almost all are sent home. This, however, does not mean that mTBI is a totally benign condition. An outcome study of patients who suffered a head injury suggested that patients with a low risk of dying, i.e. mTBI patients, are at the greatest risk of inadequate diagnosis and treatment[1]. Considering the large number of people affected, little research has been done on the assessment and treatment of this category of patients. This is also reflected by the fact that management protocols for mTBI are still under debate, which has led to considerable differences in strategies. In the last few years protocols have been published[2-4]. which might be seen as belonging to two different schools: the North American and the European. In North America, the routine use of computed tomography for the radiological assessment of mTBI patients is currently under debate, while in Europe the use of a plain skull X-ray is disputed. The primary management goal in mTBI is to identify those patients who are at risk of developing complications, specifically an intracranial haemorrhage (ICH) requiring surgery. Clinical assessment alone is inadequate for the detection of ICH[5], and radiological procedures are therefore used as additional screening tools. That patients with a skull fracture have an increased risk of intracranial haematoma is well known[6-8], but does this have practical significance? A skull fracture by itself has few clinical consequences, except in case of a depressed skull fracture. The potential clinical usefulness of radiological assessment for skull fracture depends on the ability to distinguish between patients with mTBI with and without ICH.

In order to judge the usefulness of the diagnosis skull fracture, it is important to evaluate the sensitivity and specificity of this finding as a test for the presence or absence of ICH, and to determine the prevalence of ICH in patients with mTBI. Unfortunately, sensitivity and specificity estimates reported in the literature show large variation. This may be because published studies differ in design (prospective and retrospective approaches), patient selection (admitted patients or patients seen at the emergency department) and inclusion criteria (based on Glasgow Coma Scale (GCS), loss of consciousness (LOC) or post-traumatic amnesia

(PTA)). Although ICH is mostly diagnosed by computed tomography (CT), in older studies it was diagnosed on the basis of clinical, operative, or post-mortem findings. Comparison of the data is further complicated by possible differences in threshold for a positive test result (fracture or ICH) or by differences in technical instrumentation.

Given this diversity, it is presently not possible to draw a conclusion about the value of radiography to detect skull fracture in the management of mTBI patients, and for this reason we carried out a meta-analysis of published data, using correlation analysis to identify the most important sources of variation in prevalence and diagnostic accuracy between studies, followed by use of the summary operator receiver characteristic curve technique described by Moses et al[9], to assess the effect of these potential sources of variation, and to summarize reported sensitivity and specificity estimates from the reviewed studies. Our aim was to assess the value of the diagnosis skull fracture for the diagnosis of ICH, and to summarize reported sensitivity and specificity estimates from reviewed studies. We therefore tried to account for (part of) the differences in reported sensitivity and specificity of skull fracture for the diagnosis of ICH between studies. In order to be able to estimate the predictive value of the diagnosis skull fracture, the prevalence of ICH in patients with mTBI was also estimated.

Material and methods

Literature search strategy and data collection

A systematic search for relevant original publications was conducted in Medline, Embase and Current Contents from 1966 to 1998, using the following search keys: skull fracture, skull injury, skull radiography, skull trauma, skull films, {brain or head} and {trauma or injury or injuries} and {computed tomography all subheadings}. The articles were primarily selected on the basis of the title and the abstract. Additional references were obtained from the bibliographies of the original articles. The full text of approximately 200 relevant articles was retrieved. Two sets of articles were selected, one set to estimate the diagnostic value of a finding of a skull fracture, and a second set to assess the prevalence of ICH in mTBI patients.
For the first set of papers the test under study is the plain skull X-ray for the determination of the presence of an ICH. In those studies where no skull X-rays were performed CT data were used. Papers were included if they contained data on the diagnostic value of a finding of a skull fracture by plain X-ray or CT scan in patients who suffered mTBI.

The second set of papers was selected for the assessment of the prevalence of ICH in mTBI. For these studies the standard of reference for diagnosis was the existence of ICH on CT. Only a few studies fulfilled this strict criterion, therefore we lowered the norm, and at least 50% of the patients needed to have undergone CT.

For the purpose of this study, mTBI was defined as trauma to the head, with the patient having a Glasgow Coma Scale (GCS)[10] score of 13 to 15 on initial presentation. In the selected studies the diagnosis of ICH was made by CT. If no CT scan was performed an uneventful recovery was considered a sign for the absence of an ICH. In some older studies angiography was used to diagnose ICH, and neurosurgical findings were used by some as well. An arbitrary minimum of 50 patients was required. Studies with less patients will have a statistically unreliable estimate of sensitivity, specificity, and prevalence. Studies with only paediatric or geriatric patients were not included. If the data permitted, multi-trauma patients and referrals were excluded. A standard form was used to extract relevant data from the original articles on study and patient characteristics, and various test results (Table 3.1).

Study and patient characteristics	Results
Publication year	Number of skull X-rays
Retrospective/prospective	Number of CTs
Number of referrals	True positive number (TP)
Number of patients	True negative number (TN)
Age distribution	False positive number (FP)
Mean age	False negative number (FN)
Injury severity (GCS)	Number of ICHs
Percentage with LOC and/or PTA	Number of interventions
Focal neurology	Number of deaths
Other injuries	

LOC= loss of consciousness, PTA= post-traumatic amnesia

Table 3.1: Items extracted or derived from original studies

Analysis

Prevalence of intracranial haemorrhage (ICH)

Prevalence was defined as the percentage of patients in the study with a diagnosis of ICH. Both mean prevalence weighted for sample size and unweighted mean prevalence were calculated. The weighted mean was defined as[11]:

$$\text{mean prev} = \sum(\omega_i \, prev_i) / \sum \omega_i \qquad [1]$$

$$\text{with } \omega_i = 1/(prev_i \, (1 - prev_i) / N_i) \qquad [2]$$

Calculation of the true and false positive rate

For evaluation of the diagnostic value of a skull fracture only the diagnosis of ICH was used, and not the report of a surgical intervention. This choice was made firstly because the indication for intervention differed between institutions and clear criteria were rarely given, and secondly because some investigators considered the placement of intracranial pressure monitor devices as an intervention, whereas others excluded this procedure. In those studies where no skull X-rays were performed, CT data on skull fractures were used.

From the collected data the number of true and false positive observations, and the number of true and false negative observations, were derived. True positive (TP) is defined as the finding of both a skull fracture and an ICH, false positive (FP) as a skull fracture without an ICH, true negative (TN) as the absence of both a skull fracture and an ICH, and false negative (FN) as the absence of a skull fracture in the presence of an ICH. Using these data the true positive rate (TPR=TP/(TP+FN)) and the false positive rate (FPR=FP/(FP+TN)) were calculated. The TPR equals the sensitivity and the FPR equals (1-specificity).

Correlation study to identify confounding differences between studies

The TPR and FPR are not independent. Rather there is a trade-off between the two, as is reflected in the receiver-operator characteristic (ROC) curve. Without an exact match of the study population and analysis characteristics, simply averaging these rates can be very misleading and does not provide a representative summary[12]. In order to determine the effect of interstudy differences as mentioned in Table 3.1, a correlation analysis was performed with parameter D, which is defined in the next subsection, and which is a measure for how well the test discriminates between the population with and without ICH. The Spearman correlation test was used for this analysis.

Summary operator characteristic curve

For the analysis of TPR and FPR data, as found in the different studies, we used a summary receiver operating characteristic (sROC) curve as described by Moses et al[9]. The analytic method is based on the principle that the sROC curve is conveniently represented as an approximately straight line when logit TPR is plotted against logit FPR. For statistical reasons, logit TPR- logit FPR (D) is modelled as a linear function of logit TPR + logit FPR (S).

$$S = \text{logit}(TPR) + \text{logit}(FPR) \quad [3]$$

$$D = \text{logit}(TPR) - \text{logit}(FPR) \quad [4]$$

with the logit defined as:

$$\text{logit}(x) = \ln(x/(1-x)) \quad [5]$$

S is related to how often the test is positive and D is a direct measure of how well a test discriminates between the population with an ICH and without an ICH, since:

$$D = \ln(\text{odds ratio}) \quad [6]$$

The odds ratio is a measure of association used in epidemiological studies. In diagnostic studies, the odds ratio is the odds of a positive test result in diseased patients divided by the odds of a positive test result in non-diseased patients. The higher the odds ratio, the better the test discriminates between patients with and without the disease of interest[13].

To estimate the relationship between S and D a linear model is fitted to the data:

$$D = \alpha S + C \quad [7]$$

C is a measure of the ability of the test to discriminate between diseased and non diseased individuals, and α is a measure of the extent to which D depends on the threshold for a positive test result. The higher the constant C, the better the discriminatory ability of the test. Using the fitted α and C, the relationship between TPR and FPR can be transformed back into an sROC curve.

Equation 7 can be extended with further factors (F) in order to evaluate the influence of study and population characteristics on D:

$$D = \alpha S + C + \beta F \quad [8]$$

The goodness of fit was expressed by the square of the correlation coefficient (R^2) between the observed value of D and the predicted value of D. If R^2 is 1, there is a perfect fit; if R^2 is 0 there is no linear relationship between the observed and the predicted value of D. The data analysis was performed using commercially available software (Microsoft Excel 5.0a and SPSS 6.1.1 for the PowerPC Macintosh).

Results

Description of studies

Twenty studies were identified that could be used to study the prevalence of ICH and/or the diagnostic value of the radiological detection of skull fracture for the diagnosis of ICH in adult mTBI patients. Thirteen of these studies contained data on the prevalence of ICH based on CT examinations[5, 14-25]. Table 3.2 summarizes the data of this group of studies. In 13 of the 20 studies, TPR and FPR of the finding of skull fracture in predicting ICH could in principle be calculated[17, 19-22, 25-32]. Although two studies included patients with moderate and severe head injury, these studies were nevertheless included because the majority of patients had mTBI (over 90%)[29, 30]. It seems unlikely that the small proportion of patients with moderate and severe head injury in these studies could have a major impact on the conclusions of the

meta-analysis. In five studies no skull X-rays were taken, and in these studies CT data on skull fractures were used to assess the relation with ICH. Nine studies were retrospective; the others were prospective. Table 3.3 summarizes the characteristics of these studies. Note that there is overlap between the two groups of Table 3.2 and 3.3: six studies are used for both analyses.

first author (reference)	publ. year	D	ED/ AD	N	severity (GCS)	N CT's	perc. LOC PTA	prev. ICH	surgical inter-ventions	deaths
Livingston (23)	1991	R	ED	111	14-15	111	82%	13.5%	0%	
Livingston (25)	1991	R	ED	138	14-15	75	75%	9.4%	0.7%	
Mohanty (14)	1991	R	AD	348	13-15	348	100%	3.4%	0%	0%
Rao (24)	1991	R		857	15	857		11.7%	4.3%	
Harad (5)	1992	R	ED	302	13-15	302	61%	18.2%		
Shackford (19)	1992	R	ED	2766	13-15	2166	100%	16.9%	4%	0.2%
Stein (20)	1992	R	ED	1538	13-15	1538	100%	12.9%	3.8%	
Jeret (18)	1993	P	ED	712	15	712	100%	9.4%	0.3%	0.1%
Borczuk (22)	1995	R	ED	1448	13-15	1448	80%	6.3%	0.8%	0%
Dunham (21)	1996	R	ED	2032	13-15	2032	100%	6.3%	0.4%	0.1%
Ingebrigtsen (17)	1996	R	AD	91	13-15	88	100%	8.8%	0%	0%
Holmes (16)	1997	P	ED	264	14	264	100%	12.1%	1.5%	0%
Miller (15)	1997	P	ED	2143	15	2143	100%	5.1%	0.2%	0%

ED = emergency department AD = admitted patients D= design R = retrospective P = Prospective

Table 3.2: Extracted data from the literature which were used to estimate the prevalence of ICH in mTBI.

Prevalence of ICH and correlations

The mean prevalence of ICH after mTBI was 0.1 (95% confidence interval: 0.02 - 0.18, range 0.03 to 0.18) and the weighted mean prevalence was 0.083 (95% confidence interval: 0.03 - 0.13) (Table 3.2).

Diagnostic accuracy

The sensitivity (TPR) of the finding of skull fracture in predicting ICH ranged from 0.13 to 0.75 and the specificity (1-FPR) from 0.91 to 0.995. The mean D of all studies was 3.35, and the mean sensitivity was 0.50, corresponding to a specificity of 0.97 on the summary ROC (Figure 3.1). Studies with a high TPR tended to have a higher FPR, but the fit of the sROC

curve to the observed pairs of sensitivity and specificity values was poor (R^2=0.08). Therefore, the differences in discriminatory ability between studies cannot be explained by differences in diagnostic thresholds for positive test results.

first author (reference)	publ. year	ED AD	N	D	GCS	M	N skull X-rays	N CTs	perc. LOC PTA	perc. CTs	TPR	FPR
Royal Coll (28)	1981	ED	5850	P	13-15	X	5850		*<50%*	*<50%*	.7500	.0133
Dacey (27)	1986	AD	610	P	13-15	X	583	68	100%	11%	.7222	.0817
Kraus (26)	1988	AD	2402	R	13-15	X	2402		*<50%*	*<50%*	.3876	.0854
Gorman (29)	1987	ED	12395	P	0-15	X	5484		15%	*<50%*	.7273	.0362
Masters (30)	1987		7035	P	0-15	X	4068		*<50%*	<50%	.5556	.0174
Livingston(25)	1991	ED	138	R	14-15	X	71	75	75%	54%	.4286	.0313
Shackford (19)	1992	ED	2766	R	13-15	X	423	2166	100%	78%	.6082	.2708
Stein (20)	1992	ED	1538	R	13-15	CT		1538	100%	100%	.6034	.0649
Borczuk (22)	1995	ED	1448	R	13-15	CT		1448	80%	100%	.1319	.0052
Dunham (21)	1996	ED	2032	R	13-15	CT		2032	100%	100%	.2734	.0436
Gomez (31)	1996	ED	2484	R	13-15	CT	1784	187	28%	7.5%	.5581	.0106
Ingebrigtsen (17)	1996	AD	91	R	13-15	CT		88	100%	97%	.2500	.0750
Arienta (32)	1997	ED	9830	R	13-15	X	6724	969	10%	9.8%	.5484	.0083

ED = emergency department AD = admitted patients D = study design R = retrospective P = Prospective
M = modality X= plain X-skull numbers in italic are estimates

Table 3.3: Extracted data on the value of the radiological diagnosis of skull fracture in the assessment of ICH in mTBI. These figures were used to estimate the sensitivity en specificity of the diagnosis skull fracture for the diagnosis of ICH. The sROC of these data is shown in Figure 3.1.

Consequently, an alternative explanation was needed for the variation in sensitivity and specificity. Spearman rank correlation analysis showed that the percentage of patients with LOC/PTA and the percentage of patients who had undergone CT was significantly correlated with D (Table 3.4). A model based on equation 8, which included (besides C en S) a factor representing the percentage of patients with LOC/PTA fitted the data better (R^2=0.73). Addition of a factor representing the percentage of patients who underwent CT resulted in an even better fit (R^2=0.81). This confirms that differences in patient selection and the percentage of patients in whom the diagnosis was verified by CT scans were important sources of variation between studies.

Predictor	Coefficient	p value
Percentage of patients with LOC/PTA (selection bias)	-0.6792	0.011
Percentage of CT scans (verification bias)	-0.6472	0.017
Skull X-ray compared with CT for fracture diagnosis	0.2535	0.403
Prospective studies vs retrospective studies	0.4900	0.089
Adult population vs all ages	0.0976	0.751

Table 3.4: Results of Spearman correlation analysis between potential confounding factors and D (see eq. 4 for the definition of D).

Sensitivity and specificity are not invariant to the population under study, and often they will depend on patient characteristics, e.g. patient selection. In clinical studies this is often a reflection of clinical practice. For example, a study with patients admitted for mTBI is likely to have a more severely injured population than a study with only emergency department patients. We considered patient selection as an important source of variation between the estimates of sensitivity and specificity, and the percentage of patients with LOC/PTA was the most significant selection criterion.

Selection of patients who underwent CT depending on the skull X-ray results, or on patient characteristics, will result in verification bias, also called work-up bias. We used the percentage of patients who underwent CT as a measure of verification bias. The lower the percentage of patients in whom the diagnosis of ICH was verified by CT, the higher the potential for verification bias. Although not explicitly mentioned in the studies, it is very likely that the decision to perform a CT was based on the patient assessment and/or the skull X-ray findings.

The percentage of patients with LOC/PTA was strongly correlated with the potential for verification bias. Two groups of studies were formed. The first group contained the studies in which fewer than 50% of patients had LOC/PTA and fewer than 50% of patients had a CT scan (Group 1). This group had thus a high potential for verification bias. The second group contained studies for which both percentages were higher than 50% (Group 2). There is only one study that did not fit in either of the two groups[27]. The sROC curve fitted to the data for Group 1 using equation 7, showed that in this population a relatively high TPR was reached at a low FPR (Figure 3.1). The sROC curve of data for Group 2 was lower than the sROC curve of Group 1. The mean D in Group 1 and Group 2 was 4.3 and 2.4 (p=0.016), respectively.

Summary values for sensitivity and specificity are not directly available from the analysis, but estimates can be read off the sROC curve. The mean sensitivity was 0.59 and 0.38, with corresponding specificities of 0.98 and 0.95, for Group 1 and 2, respectively.

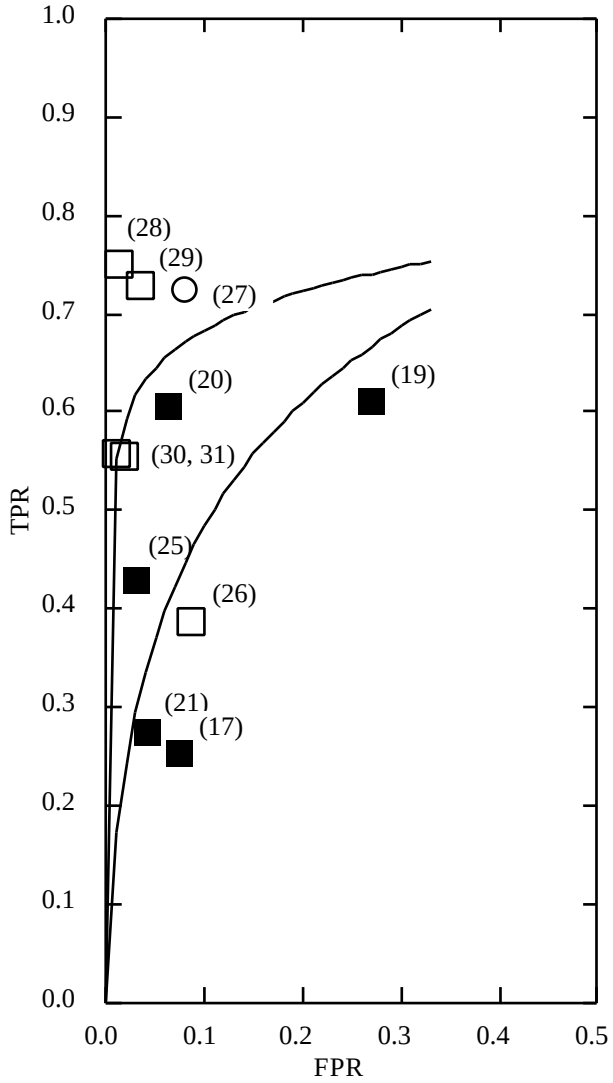

Figure 3.1: sROC curve of the diagnostic value of the radiological finding of a skull fracture for the diagnosis of ICH in mTBI. Top curve: studies with fewer than 50% of patients with LOC/PTA and fewer than 50% CTs, Group 1 (□). Bottom curve: studies with both percentages higher than 50%, Group 2 (■). ○: study with 100% patients LOC/PTA and 11% CT scans. Data are derived from the studies listed in Table 3.3.

Discussion

In this meta-analysis we investigated the value of radiological assessment for skull fracture in the diagnosis of ICH in patients with mTBI and analysed the prevalence of ICH in this category of patients.

Despite the high incidence of mTBI, relatively few well-designed prospective studies on the management of mTBI have been published. All studies found by our literature search suffered to a lesser or greater extent from bias. First, the percentage of patients with a history of LOC/PTA varied considerably, resulting in patient selection bias, and second the percentage of patients in whom the diagnosis of ICH was verified by CT was highly variable, resulting in a potential for verification bias in the majority of studies. In earlier studies only a small percentage of patients underwent cranial CT, and even nowadays patients with a GCS score of 15 but no a history of LOC/PTA seldom undergo CT. In older studies cerebral angiography, operative, and post-mortem findings were used to establish the diagnosis ICH.

The mean prevalence of ICH in mTBI patients was 0.10, the range 0.03 to 0.18, with a weighted mean of 0.083. The percentage of patients with LOC/PTA was relatively high in the studies that were used to derive this prevalence. In the studies with a low percentage of patients with LOC/PTA, fewer patients underwent CT (higher potential for verification bias). A high prevalence of ICH also has been found in studies including only patients with a GCS score of 15 and LOC/PTA[18, 24].

A strong potential for verification bias, i.e. few CT scans, leads to an overestimation of the sensitivity. Patients with a negative skull X-ray will not undergo CT, so patients with false negative results will have a higher chance of remaining undetected[33]. This bias could offer an explanation for a mean sensitivity of 0.59 for Group 1 (less than 50% CT scans), compared to a sensitivity of 0.38 for group two (over 50% CT scans). The unverified negative test results, i.e. no skull fracture, were assumed to have no ICH, and this will result in an overestimation of the specificity[33]. The data corroborate this: the specificity of 0.98 for Group 1 (higher potential for verification bias) is higher than the specificity of 0.95 for Group 2 (lower potential for verification bias). Patient selection bias and verification bias were strongly associated in the studies investigated. This made it possible to distinguish one group of studies with both a low percentage of patients with LOC/PTA and few CT scans, and a second group with a high percentage of patients with LOC/PTA and relatively many CT scans. Since verification bias affects the sensitivity[33], the sensitivity of the radiological finding “skull fracture” for the diagnosis ICH is most reliably obtained from studies with a low

verification bias (Group 2). In that group the mean sensitivity was 0.38 with a corresponding specificity of 0.95.

It should be kept in mind that a sROC curve differs from a traditional ROC curve. The ROC curve describes the relation between sensitivity and specificity in a single population, with a changing threshold. The sROC curve results from fitting a smooth line to data points representing pairs of sensitivity and specificity values from different studies and thus different populations. Therefore, the area under the curve, as a measure of overall diagnostic accuracy, cannot be determined for the sROC curve, whereas it can for the traditional ROC curve[9].

By combining the results for sensitivity, specificity, and prevalence, it is possible to calculate the positive predictive (PPV=TP/(TP+FP)) and negative predictive value (NPV=TN/(TN+FN)) of the radiological detection of skull fracture for the diagnosis ICH. With a sensitivity of 0.38 and a specificity of 0.95, as found for Group 2, and a prevalence of 0.083, the PPV is 0.41 and the NPV is 0.94. This means that if there is a skull fracture, the probability of an ICH is about 4.9 times higher than before testing. A normal skull X-ray increased the probability of no ICH from 92% to 94%. What these figures mean in clinical practice is illustrated in Table 3.5 for a fictitious group of 1000 patients. The most important conclusion of this review is that a positive skull X-ray does not predict an ICH with certainty, although the risk is definitely increased. More importantly, at a sensitivity of 0.38, a normal skull X-ray does not provide much extra information and cannot be used for ruling out the diagnosis of ICH.

	ICH +	ICH -		
skull fracture +	32	46	77	PPV= 41%
skull fracrure -	51	871	923	NPV = 94%
	83	917	1000	

Table 3.5: Findings to be expected for a fictitious population of 1000 patients with mTBI, characterized by an ICH prevalence of 0.083, in combination with a test sensitivity of 0.38 and a specificity of 0.95.

The findings of this review contradicts with data from the literature. Of the 735 patients who had an ICH in the 13 studies, only 322 (44%) had a skull fracture. Therefore, the claim that 80% of patients with ICH have a skull fracture[8] is not valid. Moreover, at a prevalence of 0.083, the probability of ICH in patients with mTBI and a skull fracture is approximately 5 times higher than in patients without a skull fracture. This is in contradiction with the 41-fold increased risk mentioned by Mendelow et al[34]. There was a strong potential for verification bias in that study, because ICH was verified in only a minority of patients. This may explain the high sensitivity of 0.75 and the high relative risk of ICH in patients with a skull fracture in

that study. Furthermore, in the studies included in this meta-analysis the prevalence of ICH in patients with mTBI presenting at an emergency department was in the order of 0.03 to 0.10, rather than the reported value of 0.003[34].

A few points need to be discussed. The first point concerns the use of both skull X-rays and CT scans (in five studies) to detect skull fracture. The skull X-ray is considered to be more sensitive for the detection of calvarial skull fracture than CT, whereas CT is more sensitive for the detection of skull base fractures. In the light of other differences between the studies, we considered this possibly not fully equivalent sensitivity acceptable. A second point concerns the use of the diagnosis of ICH as gold standard, instead of intervention or clinical course. The existence of ICH is of clinical importance as an indicator of the severity of the trauma and as a guideline for rehabilitation[35, 36]. It may very well be that the large number of ICH that went undetected until recently is in part responsible for the high incidence of post-concussional syndrome in patients with mTBI[37].

In all studies, the radiologist's report of the skull X-ray was used, while in daily practice the emergency physician or resident assesses the X-rays, and management is based on these initial findings. Thillainayagam et al showed that up to 10% of skull fractures are missed by less experienced physicians[38], who usually see most mTBI patients in many institutions. This will decrease the sensitivity of the skull X-ray even further.

The estimated mean prevalence of ICH after mTBI was 0.083. The two most significant factors explaining the inter-study difference in reported sensitivity and specificity of the existence of a skull fracture for the diagnosis ICH are the percentage of LOC/PTA patients and the potential for verification bias. We conclude that the plain skull X-ray has no place in the assessment of mTBI in adult patients. The question is not whether the detection of a skull fracture ever assists in the detection of ICH, but whether this is effective. Our analysis shows that the plain skull X-ray was ineffective as a screening tool for patients with mTBI: only slightly more than one third of ICH were detected in this way. The low sensitivity implies that if a skull fracture is not seen on skull X-ray, the diagnosis of ICH still cannot be ruled out. If patient selection increases the likelihood of ICH, CT becomes the modality of first choice.

Data from the literature also suggest that some patients with mTBI and a GCS score of 15 do not require any imaging. Two studies described a subpopulation of mTBI patients with a GCS score of 15 and no LOC/PTA or any other neurological symptoms[30, 32]. None of these patients had an ICH, and no interventions were needed. Patients with a GCS score of 15 and LOC/PTA, and patients with a GCS score of 13 and 14, require either observation, CT scanning, or both.

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- CHAPTER 4 -

QUANTITATIVE ANALYSIS OF MAGNETISATION TRANSFER IMAGES OF THE BRAIN: EFFECT OF CLOSED HEAD INJURY, AGE AND SEX ON WHITE MATTER

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Abstract

Magnetisation transfer (MT) imaging has an application in quantitative assessment of cerebral white matter. Previously published post-processing methods have inherent problems, and therefore a new analysis technique is presented. This technique was found to be more sensitive for white matter changes in patients with a post-concussional syndrome, compared to other methods previously described. Because of the potential application of this technique in longitudinal and group studies, age and sex dependence of the MT ratio (MTR) of white matter were studied. In a group of 51 healthy subjects a decrease in the mean MTR as well as an increasing distribution width of the MTR was found with increasing age. The mean MTR in males was higher than in females. These results stress the need to take age and sex into account when interpreting MTR data.

Introduction

Conventional magnetic resonance imaging techniques provide a sensitive, non-invasive method for the detection of CNS pathology. Magnetisation transfer imaging is a relatively new addition in this field. Because magnetisation transfer (MT) readily occurs in the adult cerebral white matter, this technique has the potential to increase both sensitivity and specificity of MR imaging of white matter disease [1-7]. Another advantage of MT-weighted imaging is that it is suitable for group analysis and longitudinal studies. There is a clinical application for quantitative MT imaging (MTI) in assessing the biological nature of tissue, especially of myelin in multiple sclerosis. In this field MT analysis is being increasingly used.

However, MT ratios (MTR) [8] are typically measured in a region-of-interest (ROI) and thus only a part of the brain is analysed, and the results depend on the position of the ROI. Another approach is to analyse the entire data set by presenting the MTR data as a histogram [9]. This method introduces a bias because the MT data of both grey and white matter are analysed together and a change in grey/white ratio causes a change in the MTR histogram, that is unrelated to a change in the MTR. A second issue is the effect of age and sex on MTR. Because MTI has the potential to be used in longitudinal and group studies these effects on MTR need to be determined. Two studies have been published on this subject, with conflicting findings [10, 11].

First we propose an alternative method of post-processing MT data. This method is tested on a patient population with a post-concussional syndrome. This patient group was selected because the (partially) organic aetiology of PCS is still a matter of debate, as can be illustrated by the fact that PCS is often considered a psychosomatic syndrome. If a new imaging technique would show abnormalities in this group, it probably would do so in other conditions as well. Secondly we will study the age-and sex-related changes of MTR of white matter in healthy subjects.

Material and Subjects

Methods

MR images were acquired on a Philips ACS system operating at 1.5 Tesla (Philips Medical Systems, Eindhoven, The Netherlands). MT-weighted imaging was performed with a spin-echo proton-density weighted sequence (TR 1800 msec, TE 20 msec, slice thickness 6 mm, 0.6 mm gap, field of view 180 mm, scan matrix 128x90, two excitations). Two dynamic scans

were acquired, one with and one without an off-resonance prepulse (prepulse 1000 degrees, 20 msec, 1500 Hz offset). The slice orientation was coronal and the part of the brain anterior to the splenium of the corpus callosum was included in the scan volume. The MT-weighted images were transmitted to a workstation, and a MTR image was calculated as follows:

$$MTR = (M_0 - M_p)/M_0$$ [8],

where M_0 and M_p represent the signal intensity with the saturation prepulse off and on, respectively.

In the resulting image the pixel grey scale value represents the local MTR. In a semiautomatic procedure the extra-cranial soft tissue, the skull and CSF were removed, using the software program BrainImage [12].

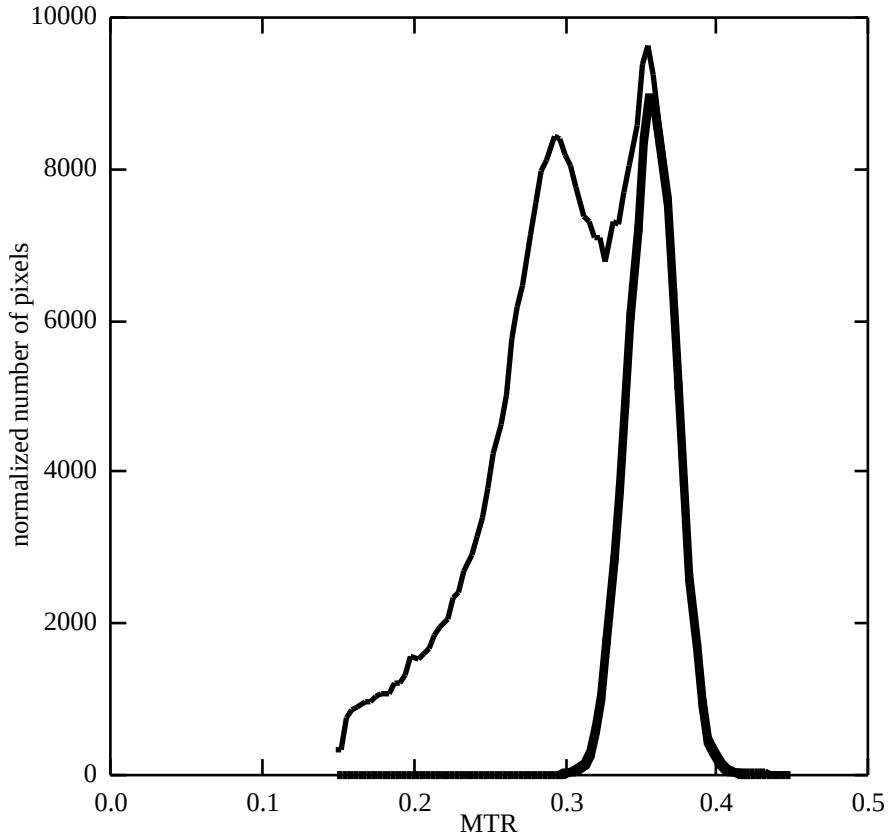

Figure 4.1: MTR histogram of unsegemented brain parenchyma (thin line) and segmented white matter (bold line).

The resulting data set was used to generate a histogram. The histogram has a characteristic shape with a gradual slope on its left side, and a steep right slope. There are two peaks: one smaller grey matter peak at MTR 0.31, and a higher one for white matter at MTR 0.36 (Figure 4.1).

First the histograms were analysed as described by van Buchem et al; the shape and location of the histogram is characterized by the location and height of the white matter peak, the mean MTR and the 25, 50, and 75 percentile of the histogram [13]. Correction for brain volume was achieved by normalizing the histogram area. Because the histogram is composed of data from grey as well as white matter, a change in ratio between these two will change the histogram peak height. Age-related changes in the grey/white matter ratio [14], as well as selective atrophy due to cerebral pathology (e.g. Alzheimer's disease, multiple sclerosis), can change the histogram this way. Theoretically the peak height is therefore a less appropriate parameter to study MTR changes. The histogram width would be a more adequate parameter, however, the left slope of the white matter section of the histogram is overlapped by the grey matter peak. Curve fitting of this histogram proved unreliable. It was found that that a third component was needed to allow for the gradual left slope, and a three component fit was highly variable and generally non-unique.

Since we are mainly interested in the white matter we performed a segmentation on the MT-weighted images. A threshold-based technique was used in combination with successive erosions and dilations to ensure incorporation of all of the white matter. The MTR of the thalamus is close to the MTR of the cerebral white matter, and consequently this structure was partly included in the white matter segment.

The segmented volume is represented in a histogram, which has a single peak. Since the shape of this histogram resembles that of a Gaussian curve quite well (Figure 4.1), we fitted the following function to the histogram:

$$y = \alpha \; e^{-(MTR-\beta)^2/(2\;\gamma^2)}$$

where α is the amplitude of the curve, β the mean MTR of the curve, and γ the curve width or standard deviation (SD). The curve fitting procedure was implemented in SPSS (SPSS Inc., Chicago, IL) using the Levenberg-Marquardt estimation method. A curve fit was considered adequate when the correlation coefficient was greater than 0.99. In addition all curve fittings were checked by visual inspection. The MTR distribution of white matter is thus characterized by the amplitude(α), the mean MTR (β) and the curve width (γ). The basic assumption in this approach is that lesions lead to tissue heterogeneity which manifests itself by broadening and a shift of the histogram. The amplitude of the segmented white matter curve depends on the white matter volume, or after normalizing the histogram, the amplitude is inversely proportional to the curve width. Either way, the curve amplitude cannot provide unambiguous information on the MTR of the white matter, for the same information is presented in the curve width.

Statistical analysis was performed using parametric and non-parametric tests as appropriate. The relation between MTR histogram characteristics, age and sex was studied with a multiple

regression analysis.

Subjects

To assess the potential of this new post-processing method, it was compared to the whole brain histogram analysis [13] using data of a group of 13 patients with a post-concussional syndrome (PCS) (7 males, 6 females, mean age 40 years, range 21-62 years) and 13 controls, matched for age and sex (7 males and 6 females, mean age 40 years, range 20-62 years). The mean interval between the trauma and the MRI study was 4 years (1-12 years), and the median initial post-traumatic Glasgow Coma Scale (GCS) [15] score was 14 (9-15). All patients met the criteria of the DSM IV classification for the diagnosis post-concussional disorder [16].

For the analysis of age- and sex-dependent changes in MTR another group of subjects was assessed. Fifty one healthy individuals (mean age of 55 years (range 21-77 years), with a normal MRI study were recruited from the general population. The mean age of the males (N=31) is 53 years (range 26-76 years), the mean age of the females (N=20) is 58 years (range 21-76 years). The difference in mean age is not significant (p=0.2). All subjects had given informed consent to participate in the study, which was approved by the Medical Ethics Committee of the University Hospital Maastricht.

Results

Histogram analysis

The comparison of the results of the two methods of histogram analysis is shown in Table 4.1. The analysis of the whole brain histogram (approach according to van Buchem et al [13]) showed a significant difference only for the histogram peak height (Table 4.1A). This parameter however depends on the grey/white matter ratio. The analysis of the segmented white matter shows the curve width to differ significantly between patients and controls (Table 4.1B). The amplitude also differs significantly between the two groups, but after histogram normalization it contains the same information as the width. Although the mean MTR for the patients is lower than for the controls, the difference is not significant.

Clearly the analysis of the segmented white matter is more sensitive for subtle white matter changes than the whole brain analysis . The parameter showing this white matter change, the curve width, does not depend on the grey/white matter ratio. This protocol was subsequently used for the second part of the study.

	patient mean (SD)	control mean (SD)	p-value
A			
histogram mean MTR	.3010 (.009)	.3050 (.010)	NS
histogram peak height	31.78 3.204	34.06 (2.12)	.044
histogram 25 perc.	.2636 (.010)	.2700 (.009)	NS
histogram 50 perc.	.3083 (.009)	.3113 (.010)	NS
histogram 75 perc.	.3439 (.009)	.3469 (.011)	NS
histogram peak MTR	.3515 (.013)	.3569 (.013)	NS
B			
curve width	.0194 (.002)	.0179 (.001)	.008
curve mean MTR	.3610 (.009)	.3631 (.011)	NS
curve amplitude	83.28 (6.50)	89.76 (4.51)	.008

Table 4.1: Histogram analysis of MTR data of trauma patients and matched controls. A) the results of the combined grey and white matter analysis, B) the results of the analysis of the segmented white matter.

Age- and sex-dependent changes

The results of the analysis of age and sex dependence are shown in Tables 4.2 and 4.3. There is a correlation of the mean MTR with age: with increasing age the mean MTR decreases. This effect is seen in both males and females. Independent of the age effect, the mean MTR for males is higher than for females (Tables 4.2 and 4.3). There is also an effect of age on the curve width, as it increases with age. No significant sex differences were found for the curve width. To assess a possible effect of head size on the mean MTR this parameter was added as a variable in the multiple regression analysis. Head size had no effect on the mean MTR (beta=0.024, p=0.82).

	age	sex	r^2
mean MTR	-.44**	-.51**	0.538
curve width	.41*	-.02	0.164

** p< .000 * p< .005

Table 4.2: Results of multiple regression analysis of parameters of the segmented white matter histogram in healthy subjects. Shown are the standardized regression coefficient (beta) and the proportion of the explained variance (r^2).

	male	female	p value
mean MTR	.3644 (.007)	.3523 (.01)	<.000
curve width	.0181 (.002)	.0183 (.002)	NS

Table 4.3: The mean of the parameters of the segmented white matter histogram in healthy subjects. Standard deviation between brackets.

Discussion

MT imaging has shown abnormalities in normal-appearing white matter [5-7]. To exploit the increased sensitivity of MT-weighted imaging the entire volume of interest should be assessed, a demand not met by ROI measurements. One of the main parameters of the whole-brain MTR histogram analysis [13], namely the histogram peak height, depends on the grey/white matter ratio. This ratio changes with age or selective atrophy of grey or white matter (e.g. Alzheimer's disease or multiple sclerosis). We therefore performed the analysis on the MTR histogram of segmented white matter. It was found that the curve width, is sensitive to post-traumatic changes and shows a higher degree of significance than the descriptive histogram parameters of the grey and white matter together. This finding corroborates the hypothesis that the post-concussional syndrome has a partial organic aetiology. At this point the value of MT-weighted imaging in individual patients with a post-concussional syndrome is still limited, because with a curve width of e.g. 0.0182 as threshold, the sensitivity and specificity are 77% and 69%, respectively.

The analysis of the segmented white matter is useful in assessing MTR changes in pathologic conditions with a multi-focal involvement of the white matter. When applying this method in group or longitudinal studies, it is important to gain understanding of the normal values and the effect of age and sex. We therefore used this new post-processing method to establish the effects of age and sex on the MTR.

Our main finding is an age dependence of the mean MTR and the curve width. The mean MTR decreases with age and the curve width increases with age. This stresses the need to take the age of individuals into account when interpreting MTR data. We also found a sex dependence of the mean MTR, males having a higher mean MTR than females. This is a new and unexpected finding. Age dependence of the MTR as observed by us was also found by Silver an co-workers [10]. Metha et al [11], however, did not find age-dependent changes of the

MTR and neither of these studies reported sex difference in MTR.

The nature of the underlying structural changes of the brain in aging and in the post-traumatic brain is different, but both changes are shown by MTR analysis. In the chronic post-traumatic brain, reduction of MTR is most likely due to increased water content and gliosis in combination with structural changes to the myelin[17]. It is unfortunate that neither for the aging brain, nor for the normal-appearing white matter is pathologic anatomical correlation available for regions with decreased MTR. Wong et al showed a decrease of MTR in normal-appearing white matter in individuals with non-specific periventricular high signal lesions as well as in the periventricular lesions [18]. They assumed that the decreased MTR is caused by an increase of the water content due to gliosis. This might be an explanation for the decrease of the mean MTR and the increase of the distribution width of the MTR with age as we found in our population.

A possible explanation for the difference between males and females is the different pattern of age-related changes in the brain. According to Murphy and co-workers, males show more frontal and temporal age-related volume loss, whereas females have age-related volume loss in the parietal lobe and the hippocampus [19]. This loss of neurons will lead to Wallerian degeneration and subsequently to a decrease in the MTR [3] and an increase of the MTR distribution width. Because the scan volume in our study encompasses the brain anterior to the splenium, these age-related changes in the white matter can explain the higher correlation coefficient of the mean MTR and the curve width with age as well as the higher significance of these correlations for males as compared to females. This does not, however, fully explain the significantly different mean MTR of males and females, as this difference is also present in healthy controls below the age of 45. Our results therefore suggest a different composition of the cerebral white matter in males and females. Previous studies did not reveal significant sex differences in the T1 and T2 relaxation times of brain [20, 21]. There is no explanation for the sex difference presently found, and these findings clearly need replication.

The pulse sequence applied by us is a spin-echo based technique with a long repetition time to decrease the effect of the T1 relaxation on the MTR. The MTRs found with our pulse-sequence are within the same range as published by others [10, 11] The MTR of the genu of the corpus callosum in our study is typically 0.37 (0.36 -0.40 [10, 11]), and the MTR of CSF is below 0.05.

The new findings reported here need to be confirmed with improved segmentation methods including co-registration of MT-weighted images with T1- and T2-weighted images. Also the patho-anatomical basis of these age- and sex-dependent changes requires further study.

Conclusion

The analysis of the MTR histogram of segmented white matter seems to be a sensitive method to assess white matter changes, with potential applications in evaluating white matter disease. We have found MTR changes with age and a difference in mean MTR between males and females. The results of our study stress the need to take the age and sex of individuals into account when interpreting MTR data.

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- *CHAPTER 5* -

BRAIN LESIONS IN PATIENTS VISITING A MEMORY CLINIC WITH POST-CONCUSSIONAL SEQUELAE AFTER MILD TO MODERATE TRAUMATIC BRAIN INJURY

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Abstract

Objective-To study the relation between brain abnormalities and post-concussional symptoms after mild to moderate traumatic brain injury and to assess the potential of quantifying brain injury by magnetisation transfer imaging (MTI), as MTI has been shown to detect microscopic brain lesions after brain trauma.

Methods-Thirteen patients with a post-concussional disorder after a mild to moderate traumatic brain injury (median GCS 14) were studied. Patients sustained the head injury one or more years before, and were recruited from a memory clinic. Patient data were compared with data from a matched control group. Both groups underwent imaging. Parenchymal brain lesions were rated on the T2-weighted images. The magnetisation transfer ratio (MTR) histogram of white mater was analysed to assess the lesion burden. The peak height of the histogram was determined as a measure of residual normal white matter. Both groups underwent a standard psychiatric and neuropsychologic examination.

Results-The patients had a significantly higher lesion volume than the matched controls ($p=0.02$). The patients had a significantly lower MTR histogram peak value (83.28 vs 89.76 $p=0.008$) than the control group. The patients performed less well on neuropsychological tests.

Conclusion-This study provides strong evidence of post-traumatic brain alterations in patients who sustained a relatively mild traumatic brain injury one or more years before presentation at a memory clinic. Histogram analysis of MTR data appears a feasible method for detecting diffuse brain injury.

Introduction

Society places a premium on effective cognitive functioning in both social and professional setting, and even a slight decline in cognitive capabilities can result in significant functional impairment. Head injury is one of the most common causes of cognitive impairment in the young, and the estimated incidence of traumatic brain injury is 200-300 per 1.000.000 people in Scotland and the U.S.[1, 2].

The majority of head injury is graded as mild, with an initial Glasgow Coma Scale (GCS)[3] score of 13 or higher at first assessment[4].

Although there is a relationship between the severity of the injury and the ultimate outcome, even mild traumatic brain injury (mTBI) without a loss of consciousness can lead to long-lasting cognitive sequelae[5-7]. Many patients complain of headache, dizziness and concentration problems after mTBI, but within a few weeks these symptoms subside and most patients return to their normal activities. However, six months after mTBI 15-29% of patients still have persistent problems[5], and these can persist for years.

Although an at least partially organic origin of the post-concussional disorder is no longer a matter of debate[4, 8], a biological marker is still missing, and little imaging evidence exists for this assumption. Oppenheimer found microscopic lesions which were probably of traumatic origin in the brains of five individuals who sustained a mTBI and died of other causes[9]. In laboratory animals mild injuries caused subtle axonal damage in the absence of gross focal lesions such as contusion or laceration[10].

Previous imaging studies with computed tomography (CT) have focused on moderate to severe brain injury, mainly because of the limited sensitivity of CT, which makes the technique less suitable for studying mild to moderate traumatic brain injury. In the acute phase of white matter injury CT has a sensitivity of only 20%[11]. Several studies have shown MRI to be more sensitive than CT[11-14], especially in the detection of non-haemorrhagic contusion and axonal injury, lesions commonly found in mTBI.

The application of new MR techniques can further increase the sensitivity of imaging subtle post-traumatic changes. We therefore performed an explorative study in patients with persistent post-concussional sequelae to assess the value of a new MR technique. Magnetisation transfer imaging (MTI) provides higher sensitivity than conventional T2-weighted images in identifying parenchymal lesions. With most conventional MR techniques image contrast is based on differences between tissue in T1 and T2 relaxation time, and proton-density. Magnetisation transfer (MT) assessment provides information about the tissue that is different from the information provided by T1 and T2 relaxation times. The physical principle of MTI is

based on the interaction between mobile protons and protons associated with macromolecules[15-17]. The MRI signal is derived from the water-associated, mobile protons, and the effect of the macromolecular protons is perceived indirectly by transfer of magnetisation to mobile protons. This transfer results in a diminished magnetisation of these water protons and therefore in a lower signal intensity on the MR image. The MT effect can be quantified by acquiring two images, one with and one without a specific prepulse that maximizes the MT effect, and calculating a suitable ratio (MTR). Myelin, which is the main constituent of white matter, is considered to be an important macromolecular structure in MT, and loss of macromolecular structure decreases the MT effect. A decrease in MTR is found in the early stages of Wallerian degeneration, where conventional imaging sequences fail to detect abnormality[18]. MTI also detects lesions in normal-appearing white matter in multiple sclerosis and metastasis[19-21]. A recent animal study has shown that MTI is sensitive for post-traumatic lesions: areas in the brain that had an altered MT but a normal appearance on T2-weighted scans were found to have axonal disruption and secondary degenerative changes on histopathologic examination[22]. Typically the MTR is analysed in a two-dimensional region of interest. Although this will show focal lesions, diffuse brain abnormalities, which are commonly seen in post-traumatic patients, are not easily assessed in this way. Histogram analysis allows for the assessment of a volume of brain tissue, and for the quantification of both high-contrast lesions and diffuse abnormalities in normal appearing white matter[23, 24]. This method of analysis fully exploits the potential of MTI to detect microscopic lesions.

The present study was conducted: (1) to study the relation between structural brain abnormalities and symptoms after mild to moderate traumatic brain injury; and (2) to assess the potential of MTI for quantifying brain injury. We selected a population with a high a priory risk of abnormalities in order to asses the applicability of this new technique. The subjects were patients with a post-concussional disorder (DSM IV[25]) who presented at a university based memory clinic, and matched controls.

Subjects and methods

Subjects

Patients with a post-concussional disorder who attended the Memory Clinic of the University Hospital Maastricht were enrolled in the study. The criteria of the DSM IV classification were used for the diagnosis post-concussional disorder[25]. These include: a history of head trauma that caused significant cerebral concussion, evidence from neuropsychological testing or quantified cognitive assessment of difficulty with attention or memory, and three or more of the following complaints: becoming fatigued easily, sleeping disorder, headache, dizziness, ir-

ritability, anxiety, depression, affective lability, personality changes or apathy. These complaints must have commenced, or substantially worsened after the trauma, and have affected social or professional functioning. All patients underwent a standardized diagnostic assessment, including psychiatric, neurological and psychological examinations, as described elsewhere[26]. Psychiatric diagnoses were made according to DSM IV criteria[25], as well as by means of the Hamilton Rating Scale for Depression[27] (HRSD).

All patients had sustained a closed head injury at least one year before they took part in this study. The GCS score[3] recorded in the patient file was used to assess the severity of the trauma. Patients with other neurological and major psychiatric disorders, as well as substance abuse, were excluded from this study. Patients who sustained significant extra-cranial injury were also excluded from this study. A healthy control group, matched pairwise for sex and age, without neurocognitive complaints was recruited from the general population by advertisement in newspapers. All subjects gave their written informed consent to participate in the study, which was approved by the Medical Ethics Committee of the University Hospital Maastricht.

Neurocognitive testing

Both patient and control groups underwent a standardized neuropsychiatric and neuropsychological examination. The neuropsychological assessment included tests for verbal memory, for basic cognitive speed, and speed of complex operations[28-31]. These tests were used because earlier research has indicated that these cognitive aspects are most relevant in post-concussional syndromes[32, 33]. The test results were reduced to three variables by making composite scores for memory, sensorimotor speed, and cognitive speed[34]. Normative data for different age groups were used as reference when transforming the scores into z-scores (for z-score conversion see[28, 34]).

Neuroimaging

MR images were acquired on a Philips ACS system operating at 1.5 Tesla. A scout sequence was used to align the subsequent scans. The MR examination protocol consisted of an axial proton-density and T2-weighted fast spin-echo (FSE) sequence and an axial T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence (Table 5.1). MTI was performed with a spin-echo proton-density weighted sequence, with and without an off-resonance prepulse (Table 5.1). The patients were also studied with a T2-weighted gradient echo sequence (T2 FFE) to detect haemosiderin depositions.

	axial dual T2 turbo spin-echo	axial T2 FLAIR spin -echo	coronal proton density dynamic MTC
section thickness (mm.)	5	5	6
no. sections	24	24	22
section gap (mm.)	.5	0.5	0.6
field of view (mm.)	230	230	180
matrix (pixels)	256x205	256x230	128x90
repetition time (msec.)	3000	6000	1800
inversion time (msec.)	-	2000	-
echo time (msec.)	23/150	150	20
flip angle (deg.)	90	90	90
echo train length	12	22	-
number of signal averages	2	4	2
scan time (min.:sec.)	3:24	7:48	5:42
prepulse			1000^{0}, 20 msec., -1500 Hz

Table 5.1: Scan parameters

Lesion analysis

The hardcopies the MRI studies were screened for abnormalities by a neuroradiologist. The lesions were scored on a semi-quantitative scale as proposed by Scheltens et al[35]. This formal rating scale uses a score of 0-6 with separate scores for each of the cerebral lobes, the periventricular, the subcortical regions, and the infra-tentorial brain structures. The maximum possible cumulative score for the cerebrum is 24, the maximum score for one region is 6. Perivascular spaces were disregarded. The rater had no knowledge of the clinical data. The reliability of this rating scale was assessed in a previous study[36].

Image processing

The MT images were transmitted to a separate workstation (PowerPC, Apple Macintosh), and we used our own software to calculate an MTR image according to:

$$MTR = (M_{off} - M_{on})/M_{off}$$ [37],

where M_{off} and M_{on} represent the signal intensity with the saturation prepulse off and on, respectively. In the resulting image the pixel grey scale value equals the local MTR. From the coronal data set, the slices anterior to the splenium of the corpus callosum were selected for further analysis. This was to ensure that the data set of each individual included the same

anatomical regions.

MTR is typically measured in a region-of-interest (ROI), and the results depend on the position of the ROI. Another approach is to analyse the entire data set by presenting the MTR data as a histogram[23]. This method introduces a bias because the MT data of both grey and white matter are analysed together and a change in grey/white ratio causes a change in the MTR histogram, that is unrelated to a change in the MTR. A new post-processing technique to circumvent this problem has been developed. White matter is segmented from CSF, grey matter and extra-cerebral tissue and subsequently the histogram of the normalized white matter MTR distribution is analysed. To characterize this histogram we fitted a Gaussian function to the data, and thus the MTR histogram is characterized by the amplitude, the mean MTR and the curve width[24].

Statistics

Statistical analysis was performed using nonparametric and parametric tests as appropriate. Significance was tested with a two-tailed test, and a level of 5% was considered significant.

Results

Demographics

Thirteen patients (seven men, six women) met the criteria for inclusion in the study. The mean age was 40 years (range 21-62 years). The mean interval between the trauma and presentation was 4 years (1-12 years), and the median initial GCS score was 14 (9-15). The median duration of post-traumatic amnesia was 2 hours, the median duration of loss of consciousness was 10 minutes. Subjects and controls were comparable with regard to level of education on a 7 point scale[38] (patients 3.9, controls 4.2, $p > 0.1$). Although many patients had complaints of mildly lowered mood, none except one patient had a score on HRSD in the range of clinically relevant depression (i.e. score > 17) (mean HRSD 12.4, range 6-19). The patient with a HRSD score of 19 had complaints of affective lability, lowered mood and anxiety, but had no other clinical signs of major depressive disorder.

The subjects of the control group were matched for age and sex (mean age 40 years, range 20-62 years, seven men and six women) and none had sustained a head injury.

Neuropsychological test

The combined ratings for memory resulted in a z-score of -1.07 (SD 0.98) for the patients and 0.03 (SD 0.93) for the controls. The z-scores for sensorimotor and cognitive speed were -4.45

(SD 3.59) and -2.60 (SD 2.83) for patients and -0.32 (SD 0.71) and -0.16 (SD 0.73) for controls. The results of the two groups were significantly different on all three cognitive domains (t-test, $p \leq 0.01$).

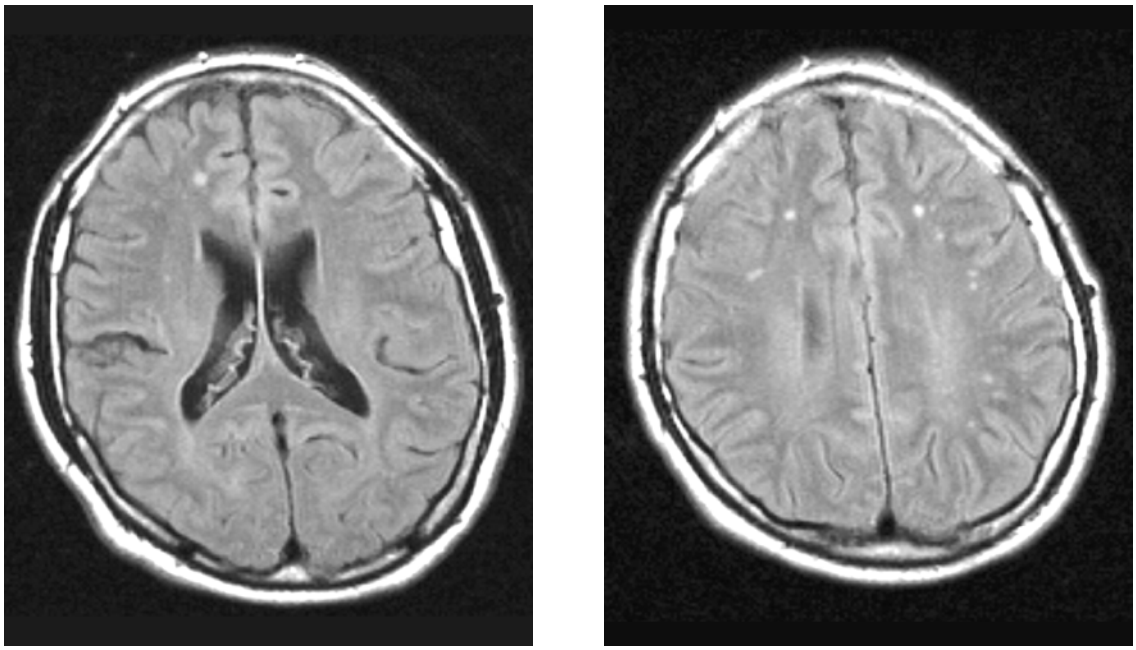
Lesions

The analysis of lesions focused on the frontal, temporal, occipital, and parietal lobes. There were too few lesions in the subcortical grey matter and the infra-tentorial brain to make any inference. In one patient only the MTI sequence was performed and thus there was no information available about parenchymal lesions. The T2-weighted FFE sequence showed no haemosiderin depositions. The cumulative scores for the different regions showed the fronto-temporal region to be affected most often (Table 5.2, Figure 5.1).

	controls N=13	patients N=12
frontal	7 (4)	26 (8)
parietal	6 (4)	12 (4)
occipital	1 (1)	5 (3)
temporal	0 (0)	12 (5)

Table 5.2: Cumulative score of parenchymal lesions, between brackets the number of affected subjects.

Patients had a significantly higher prevalence of parenchymal lesions than controls (77% vs 38%, Chi-square test, $p<0.05$). The median score for parenchymal abnormalities in the patient and control groups was 3 and 1, respectively, this difference was significant (Wilxocon signed-ranks test $p=0.02$). To assess the effect of age on the volume of parenchymal lesions, the data for the patients and controls were combined in an analysis of variance. There was a significant main effect of patient vs control ($p=0.013$), and an independent effect of age ($p=0.014$).



a b

Figure 5.1: T2-weighted FLAIR images of a 41 years old male who suffered a mild traumatic brain injury four years previously and who presented with neurocognitive complaints. Bilateral focal areas with increased signal are seen in the frontal white matter as well as in the left parietal white matter. The T2-weighted gradient-echo images (not shown) did not reveal focal signal loss, there is no haemosider deposition.

Magnetisation transfer data

The mean histograms for controls and patients are shown in Figure 5.2. The curve amplitude of the white matter histogram was 83.28 for the patients and 89.76 for the controls (Table 5.3). This difference was statistically significant (t-test, p=0.008). The width also differs significantly between the two groups, but after histogram normalization it contains the same information as the amplitude. The mean MTR for the patients is lower than for the controls, the difference is not significant.

Interaction with neurocognitive and clinical parameters

There was no correlation between neurocognitive parameters and the lesion volume or the histogram parameters. There was a significant correlation between the lesion volume and the duration of unconsciousness (Pearson 0.63 p=0.038), and the correlation with duration of post-traumatic amnesia approaches significance (Pearson 0.61 p=0.06).

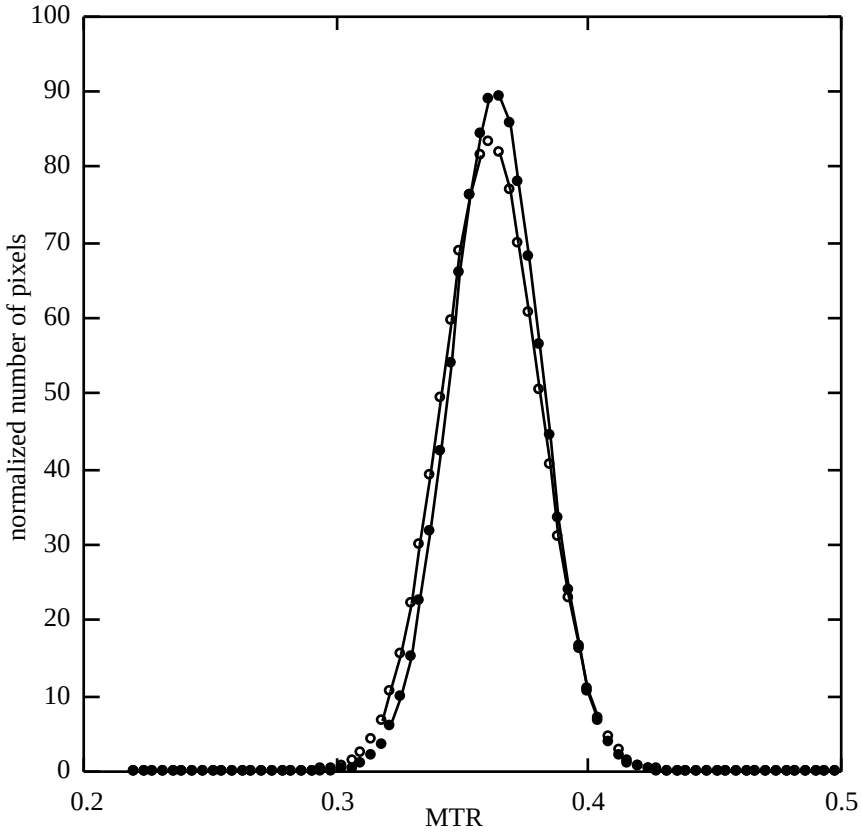


Figure 5.2: The white matter MTR histogram of the patient group (○) and of the control group (●). Note the decrease amplitude and the shift to the left of the histogram of the patients.

	patient mean (SD)	control mean (SD)	p-value
curve width	0.0194 (.002)	0.0179 (.001)	0.008
curve mean MTR	0.3610 (.009)	0.3631 (.011)	NS
curve amplitude	83.28 (6.50)	89.76 (4.51)	0.008

Table 5.3: White matter MTR histogram parameters of the patient and control group.

Discussion

The main finding of our study is an increased lesion load in patients one year or longer after a mild to moderate traumatic brain injury, as evidenced by the higher number of focal lesions, as well as a significant decrease of the peak height in the MTR histogram in patients with post-concussional symptoms as compared with matched controls. Even in a small group of

only thirteen patients these differences were significant.

Demyelination, oedema, and post-traumatic changes decrease the MTR[19, 20, 22], causing a shift toward the left and flattening of the histogram peak. The decrease in the peak height of the MTR histogram of our patients can therefore be explained by the existence of macroscopic and microscopic lesions. Histopathologically these lesions are most likely areas of focal axonal loss, demyelination, and astrocytosis[39]. Animal studies have shown that mTBI causes mitochondrial swelling, oedema, and subtle axonal damage in the absence of gross focal lesions, contusions or laceration[10, 40]. This has also been shown in patients who died of a non-CNS related injury shortly after a minor head trauma[9].

Our analysis of focal lesions shows that patients with a post-concussional disorder have a higher lesion load than matched controls and that these lesions are mainly located in the frontal and temporal regions. This last finding is in agreement with previous studies[41-44]. The prevalence of focal lesions in our patient group is 77% as compared to 38% in the matched control group. This is high considering the time elapsed between the trauma and imaging. Parenchymal lesions decrease in size and number after the trauma, especially during the first 3 months[44]. MRI studies performed shortly after mTBI show a prevalence of abnormalities ranging from 30 to 77%, depending on the patient selection and scanning technique[14, 44, 45]. The present patient population features a DSM IV classified post-concussional disorder with neurocognitive complaints, who presented at a university based memory clinic. This strong selection bias might explain the relatively high prevalence of frontal-temporal lesions. Even though the controls had a prevalence of 38% of parenchymal lesions, the patients had both a higher prevalence and a higher lesion volume. It is an interesting finding that differences between patients and controls were larger in the older population. The poor correlation of imaging results and neurocognitive and clinical parameters is probably due to the small sample size.

Our results cannot be extrapolated to all patients with post-concussional symptoms without due consideration. Although we careful matched for age and education, and excluded patients with concomitant injuries and neurologic or psychiatric disorders, we cannot exclude the effect of other confounding factors, such as litigation. A prospective study with a larger unselected sample including patients with mTBI but no complaints is needed to confirm our findings.

Interestingly, recent evidence from experiments with healthy individuals who had sustained a mTBI a long time ago shows that these subjects suffer from impaired cognitive functioning compared to that of healthy subjects who had not sustained traumatic brain injury[32, 46]. This suggests that mTBI may have long-term subclinical effects which become apparent upon neurocognitive testing. It is tempting to hypothesize that these subtle dysfunctions are due to

changes in brain structure similar to those found in our patient group.

Conclusions

This study provides strong evidence of post-traumatic brain alterations in patients who sustained a relatively mild traumatic brain injury one or more years before presentation at a memory clinic with cognitive complaints. Our results support the hypothesis of an at least partially organic aetiology for post-concussional symptoms in these patients. We are currently carrying out a prospective study to investigate this matter further.

Histogram analysis of MTR data seems a useful method for the detection of diffuse brain injury. The method has the potential to detect macroscopic as well as microscopic lesions and, as every automated analysis, is less prone to observer variation.

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- CHAPTER 6 -

MRI, SPECT AND NEUROCOGNITIVE PERFORMANCE IN MILD TRAUMATIC BRAIN INJURY

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Abstract

Introduction-Mild traumatic brain injury (mTBI) is a common neurological disorder and a common cause of neurocognitive deficits in the young population. Most patients recover fully from mTBI, but 15-29% of patients have persistent neurocognitive problems. The aetiology of this post-concussional syndrome is still a matter of debate. Although a partially organic origin is considered likely, little brain imaging evidence exists for this assumption. Most studies so far have focused on moderate and severe head injury, using computed tomography (CT). However, magnetic resonance imaging (MRI) is much more sensitive to post-traumatic changes. The aim of the present study was to establish the prevalence of post-traumatic lesions in mTBI patients on MRI, and to assess the relation between these imaging findings and post-traumatic symptoms. Secondly, the value of early post-traumatic brain single-photon emission computed tomography (SPECT) in the assessment of mTBI was explored.

Subjects and methods-Twenty-one consecutive patients aged under 50 with mTBI were included in the study. Patients had a MRI examination, a Tc99m-HMPAO brain SPECT and neurocognitive assessment within five days after injury. Neurocognitive follow-up times were 2 and 6 months after injury, and MRI was repeated after 6 months. Lesion size and brain atrophy were measured on the MRI studies. The neurocognitive test results were combined in one compound z-score.

Results-Twelve out of twenty one patients had abnormal MRI findings (57%), and eleven out of eighteen patients had abnormal SPECT findings (61%). Patients with an abnormal MRI showed statistically more brain atrophy than the normal group. The neurocognitive performance of all subjects was within the normal range. There was no difference in neurocognitive performance between patients with normal and abnormal MRI findings. Patients with abnormal MRI findings only showed significantly slower reaction times on a reaction time task. The results of SPECT imaging did not reveal an association with neurocognitive tests results either. Seven patients had persistent neurocognitive complaints and one patient met the criteria for a post-concussional syndrome.

Conclusion-Brain lesions are common after mTBI; up to 77% of patients may have abnormal findings either on MRI or on SPECT, and these lesions may lead to brain atrophy. There is no correlation between neuroimaging findings and neurocognitive outcome.

Introduction

Traumatic brain injury is the neurologic disorder with the highest incidence in the young population, and the most common cause of cognitive impairment in this group. The Head Injury Task Force of the National Institute of Neurologic Disorders has estimated that there are 2,000,000 cases of head injury in the USA annually, of which approximately 80% sustain a mild traumatic brain injury (mTBI)[1]. Many patients complain of headache, dizziness, memory impairment and concentration problems after mTBI, but in most patients these initial symptoms subside within a few weeks. Some patients, however, continue to report a variety of symptoms, such as headaches, dizziness, memory and concentration problems, and irritability, long after the of the mTBI. It has become clear that mTBI can cause long-lasting sequelae, and after six months 15-29% of patients still have appreciable complaints[2]. Although the aetiology of these post-concussional symptoms is still controversial, the persistent complaints are considered a syndrome and as such the post-concussional syndrome (PCS) is under study for classification in DSM-IV[3]. The annual incidence of patients with persistent complaints after mTBI is at least 240,000 in the USA, and is estimated at 7000 in the Netherlands.

Detecting patients at risk of developing of PCS is of potential interest, because neurobehavioural rehabilitation reduces the risk of persistent symptoms, and treatment failure is common if symptoms persist after 3-6 months[4]. It is not possible to detect patients at risk of developing of PCS based on clinical presentation[5, 6]. Although an at least partially organic origin of the post-concussional disorder is no longer a matter of debate[7, 8], a biological marker is still missing, and little imaging evidence exists for this assumption. Previous brain imaging studies with computed tomography (CT) have focused on moderate to severe brain injury. Because of the limited sensitivity of CT, this technique is less suitable for studying mTBI. In the acute phase of white matter injury, for example, CT has a sensitivity of only 20%[9]. Several studies have shown MRI to be more sensitive than CT[9-12], especially in the detection of non-haemorrhagic contusion and diffuse axonal injury, lesions commonly found in mild traumatic brain injury. Little is known about the relationship between morphologic damage and the outcome of patients after mTBI. Levin et al[13] published a longitudinal study on patients who had sustained a mild to moderate head injury, using neuroimaging and neurocognitive follow-up. They found heterogeneity in the relation between MRI findings and neurocognitive test results. Since then, new sequences have been introduced in MRI, such as fluid attenuated inversion recovery (FLAIR)[14], and fast field echo T2-weighted imaging (FFE T2)[12]. These new techniques will further enhance the sensitivity of MRI for post-traumatic changes.

MRI provides information on structural cerebral damage, while techniques such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) may provide insight into functional effects of brain injury. These techniques can identify abnormalities of cerebral perfusion, and therefore detect lesions not seen on MRI. Subacute and late SPECT brain imaging has been found to reveal more abnormal findings than CT and MRI in mTBI patients[15-17], and Jacobs et al found a correlation between post-concussional symptoms in mTBI patients and abnormal SPECT findings for upto a year after the trauma[18]. However, to date no data are available on the value of early SPECT imaging in mTBI patients.

The aim of the present study was to establish the prevalence of post-traumatic lesions in mTBI patients on MRI, and to assess the relationship between these imaging findings and post-traumatic symptoms. In addition, the value of early post-traumatic brain SPECT in the assessment of mTBI was explored.

Materials and methods

Consecutive patients aged under 50 presenting at the emergency department with uncomplicated mTBI were included in the study. Patients had to meet the following criteria: closed head injury, Glasgow Coma Scale (GCS) score of 14 or 15[19], loss of consciousness for less than 20 minutes and post-traumatic amnesia for less than 6 hours. Patients who underwent anaesthesia or who had sustained significant extra-cranial injury were excluded. Patients with previous head injuries, alcohol or other substance abuse, and patients with major psychiatric, neurological or medical problems were also excluded. To prevent interference from aspecific white matter lesions, patients with diabetes mellitus or hypertension were excluded as well. The protocol specified completion of a cerebral MRI examination, a Tc99m-HMPAO brain SPECT, and neurocognitive assessment within five days, but not earlier than two days after the trauma. All studies were performed on the same day, always beginning with the neurocognitive examination. Neurocognitive follow-up times were at 2 and 6 months after injury, and MRI was repeated after 6 months. The study was approved by the Medical Ethics Committee of the University Hospital Maastricht, and all patients gave their informed consent.

Image acquisition

MR images were acquired on a Philips ACS system operating at 1.5 Tesla (Philips Medical Systems, Eindhoven, The Netherlands). A scout sequence was used to align the subsequent scans. The MR examination protocol consisted of three pulse sequences; axial dual T2-weighted fast spin-echo (TR 3000, TE 23/120, ETL 12, matrix 265x186, NSA 2), with 24 slices, 5 mm

thick and 10% interslice gap, axial T2-weighted fluid-attenuated inversion recovery (FLAIR) (TR 6000, TE 150, ETL 22, TI 2000, matrix 256x230, NSA 4), with 24 slices, 5 mm thick and 20% interslice gap; and axial T2*-weighted gradient echo to detect haemosiderin depositions (TR 750, TE 40, flip angle 10, matrix 256x204, NSA 2), with 25 slices, 5 mm thick and 10% interslice gap.

SPECT acquisition and quantification was done as described by Matsuda et al[20]. The patient was left for 15 minutes in a quiet, half-dark room, and after the pulse rate had dropped below 100 beats per minute, 740MBq of Technetium^{99m} Hexamethylpropylamine-Oxime (Tc^{99m}-HMPAO) (Ceretec, Amersham, England) was administered intravenously. On a single head camera (Siemens Gammasonics, Hoffman Estate, IL, USA) a 128 x 128 matrix was used to image patient's head and heart and 110 images of 1 second duration were obtained. These images were used to calculate the brain perfusion index according to Matsuda et al[20]. Fifteen minutes later brain SPECT was performed with a triple-head gamma camera (Siemens Gammasonics, Hoffman Estate, IL, USA) (matrix size 128 x 128, high resolution collimators, 3 x 30 views). Images were reconstructed using a Butterworth filter of the order of 5 or 6, and a cut-off value of 0.35-0.45 of the Nyquist frequency. Chang's attenuation correction was applied, using an attenuation coefficient of 0.12/cm. Transverse images of the brain were reconstructed parallel to the orbitomeatal line. Applying the brain perfusion index allowed hemispheric blood flow and regional cerebral blood flow to be calculated with a program based on the method described by Matsuda et al[20]. The Siemens brain quantification program was used to determine mean bloodflow. A side - to - side difference between regions of more than 10% was taken as a significant sign of reduced or luxury blood flow due to the trauma. The MR images were independently read by two neuroradiologists, the SPECT studies by a neuroradiologist and a nuclear physician.

Image postprocessing

The axial T2-weighted fast spin-echo images were processed using BrainImage[21] on a Macintosh G3 computer (Apple Computer, Cupertino, CA). The raw data were imported and corrected for signal inhomogeneity. Subsequently the extracranial tissue and the calvaria were removed from the images, using processing tools available in BrainImage. The inner table of the skull was used as the landmark for the separation. The resulting image contained only brain parenchyma and CSF, and all pixels were assigned to one of these two categories. Subregions of interest included the lateral ventricles, including the temporal horn. Because the initial segmentation step had already identified the interface between CSF and brain parenchyma, precise tracing of the ventricular system was not necessary, as long as no other CSF-containing structures were included in the region of interest. Care was taken to analyse comparable slices, because subjects were scanned with an interval of six months. Fifteen consecutive

slices were analysed from the floor of the anterior skull base to the vertex. The total brain volume was determined by summing all brain pixels and multiplying that by the voxel dimensions. The same procedure was used to determine the ventricular volume. The ventricle-to-brain ratio (VBR) was calculated, and the ratio measured on the initial scan was divided by the ratio from the scan performed at 6 months (tVBR). In five patients, tVBR could not be determined; three patients were lost in follow-up, and in two patients the raw data of the axial T2-weighted images were unavailable. A decrease in tVBR is a measure of brain atrophy. The intra-observer variation for VBR determined on a subset of four scans was 0.99.

The volume of parenchymal lesions was assessed on the T2-weighted FLAIR and T2*-weighted FFE images. A local threshold algorithm of BrainImage was used to segment the lesions. High signal lesions were measured on the T2-weighted FLAIR images, while low-signal lesions, containing haemosiderin, were measured on the T2*-weighted FFE images. The lesion volumes were determined using a method analogous to that used for the brain volumes.

Neurocognitive testing

The choice of neurocognitive tests was based upon earlier studies in mTBI patients[22-24]. The following tests were used:

-The Visual Verbal Learning Test (VVLT). This memory test is a visual version of the Rey Auditory Verbal Learning Test[25]. In three consecutive trials, a list of 15 words has to be memorized and reproduced. The VVLT also involves a delayed recall after 20 minutes, thus enabling measurement of memory retrieval. The dependent variables are the total number of words recalled over the three trials (VVLTtot), and the recall performance after 20 min (VVLTrec).

-Stroop Colour Word Test (SCWT)[25]. The SCWT has often been used to test selective attention, mental speed, and interference susceptibility[26]. The test uses three cards displaying forty stimuli each; colour names (SCWT I), colour patches (SCWT II), and colour names printed in incongruously coloured ink (SCWT III). The dependent variables are the times needed to read (SCWT I), to name the colour of the patches (SCWT II) or the printing ink (SCWT III).

-Concept Shifting Test (CST). This test is an adaptation of the Trail Making Test, which is a test of visual conceptual and visuomotor tracking and has been used to measure the ease of shifting between concepts in ongoing behaviour[26]. The CST consists of three subtasks. In each task, 16 small circles are grouped in a large circle. In the first part the circles contain numbers (CSTA), in the second part letters (CSTB), and in the third part both numbers and letters (CSTC). The circles are in random order and in each subtask subjects are requested to cross out items in the correct ascending order. The depended variable is the time needed to complete the task.

-Letter Digit Substitution Test (LDST). This test is a modification of the procedurally identical Symbol-Digit-Modalities Test[25, 27]. The subjects are supplied with a code at the top of a page, which links a digit to a letter. Subjects have limited time to fill in blanks which correspond to the correct codes. The coding test is used to measure the speed of processing of general information. The dependent variable is the total number of digits written correctly in 60 seconds.

-Fluency[27]. This test can be regarded as a measure of the adequate, strategy-driven retrieval of information from semantic memory. Fluency is defined as the ability to produce as many words as possible in a given category, within a fixed time span. Subjects are requested to name as many animals as possible within one minute (dependent variable).

-The (MCRT) is a computer task in which reaction times are studied as a function of the complexity of the task requirements[28]. The dependent variable is the median incompatible choice reaction time in msec. This test was only performed at the last follow-up, after six months.

The results of the various tests were transformed to a standard z-score[25, 29] using reference values from the Maastricht Memory Study[30] and the Maastricht Aging Study[27]. In order to prevent type I error, we combined the scores of the different tests into a single z-score using the following formula:

$$(zVVKTtot + zVVLTrec - zCSTA - zCSTC - zSCWTI - zSCWTIII + zLDST + zfluency)/8$$

Combined z-scores for the initial assessment, as well as for the follow-up at 2 and 6 months were calculated.

At two and six months patients filled out a 28-item questionnaire on post-traumatic symptoms[31]. The results were reduced to a single score. The outcome has been found to correlate with persistent symptoms after mild traumatic brain injury[31].

Results

Twenty-one subjects were included in the study, 9 females and 12 males. The mean age was 22.8 years (SD 7.65, range 15-42 years). The mean education level was 5 on a scale from 1 (only primary school) to 8 (university education), and the mean number of educational years was 13.5 (range 9-23). The mean GCS score at presentation was 14.48 (SD, 0.6 range 14-15) with a mean duration of unconsciousness of 4 minutes (SD 4.40, range 0-15 minutes), and a post-traumatic amnesia period of 67 minutes (SD 83.76, range 0-300 minutes) (Table 6.1). The accidents were traffic-related in 16 cases, sports-related in 4. One patient had fallen from the stairs.

Twenty-one patients had the initial MRI and eighteen patients underwent the brain HMPAO SPECT. No patient required neurosurgical intervention. One subject only had a follow-up examination at six months, while three subjects were lost to follow-up.

Acute Imaging

Eleven patients had an abnormal SPECT (61%) and 12 an abnormal MRI (57%). Four patients had normal MRI as well as normal SPECT findings, and in seven patients both examinations were abnormal (Figure 6.1). The SPECT study alone was abnormal in an additional four patients. In these patients, the SPECT images showed hypoperfusion in the frontal and parietal lobes, and also in the thalamus in one subject. MRI revealed three additional abnormal subjects. In two of these patients the MRI showed subtle abnormalities on either the T2*-weighted images or the FLAIR image. The third patient had multiple post-traumatic lesions. The agreement between MRI and SPECT studies was, on the whole, poor; the kappa value was 0.20. To assess the correlation between MRI and SPECT with respect to lesion location, all lesions were assigned to one of four brain quadrants; frontobasal, high frontal, temporal or parietal. Lesions in other location were disregarded. If at least one lesion in a quadrant was seen, both on MRI and SPECT, it was rated as an agreement. The kappa value of the four quadrants were 0.35 for the frontobasal region, 0.44 for the high frontal region, 0.42 for the temporal region, and 0.22 for the parietal region. The mean kappa for the four regions was 0.36.

The FLAIR images revealed more and larger lesions than the T2*-weighted images. In some instances, small haemorrhagic lesions located in the white matter (diffuse axonal injuries) were seen only on the T2*-weighted images. The mean lesion volume for patients with abnormalities was 3.61 ml on the FLAIR images (SD 5.9 ml, range 0.00-18.46 ml), and 1.72 ml on the T2*-weighted images (SD 2.93 ml, range 0.00-9.44 ml). This difference in lesion volume was statistically significant (paired t-test, $p=0.05$). Two patients had an extra-cerebral haemorrhage. The majority of lesions was found in the frontal lobe (42 lesions) and temporal lobe (16 lesions). One cerebellar lesion was found, but no brainstem lesions. Patients with abnormal MRI findings did not differ from patients with normal MRI findings as regards to age, education and trauma severity parameters (Table 6.2).

age/sex	edu. level	edu. years	GCS	LOC PTA min	SPECT MRI	lesion vol. FLAIR ml	lesion vol. T2* ml	N lesions	NCE z-score acute	NCE z-score 2 m	NCE z-score 6 m
30/m	6	16	14	1/300	1/0	0	0	0	0.18		0.32
15/f	4	10	15	10/15	0/0	0	0	0	-0.20	0.13	0.16
15/f	3	9	14	5/5	0/0	0	0	0	0.19	0.66	1.03
16/f	5	10	14	/60	/1	0.14	0	1	0.74		
21/m	4	14	14	5/20	0/1	0	0.16	1	-1.19	-0.38	-0.30
22/f	4	10	14	2/30	0/0	0	0	0	-4.29	-1.23	0.84
21/m	4	14	15	15/30	/0	0	0	0	-0.57	0.14	-0.17
23/m	5	15	15	0/15	1/1	0.40	0.62	6	0.14		
21/f	4	13	15	5/15	1/0	0	0	0	-0.80	-0.35	-0.21
36/m	2	10	14	9/20	1/1	18.46	9.44	9	-0.43	0.74	0.55
16/f	5	11	14	0/1	0/1	12.41	5.74	8	-0.88	-0.35	0.15
23/m	4	14	15	/60	1/1	2.55	1.81	10	-0.05	0.28	1.18
19/m	6	13	15	1/30	0/0	0	0	0	0.72	0.66	1.14
21/f	8	16	15	1/15	0/1	0.24	0	1	0.26	0.56	1.07
19/m	4	13	14	9/180	1/1	1.63	0.16	7	-1.87	-1.06	-0.02
42/m	8	18	14	9/240	/1	0.58	0.53	4	-1.62	-0.88	0.02
39/m	8	23	14	0/180	1/0	0	0	0	0.44	0.49	0.58
17/m	4	12	14	1/60	1/1	1.06	0.21	6	-0.23	-0.03	0.19
24/m	6	16	15	1/60	1/0	0	0	0	0.40		
20/m	6	14	15	3/0	1/1	5.78	2.01	5	0.63	0.83	1.10
19/f	6	13	15	0/0	1/1	0.01	0	1	0.01	0.75	0.80

PTA=post-traumatic amnesia LOC=loss of counsciousness NCE=neurocognitive examination

Table 6.1: Demographic data, trauma characteristics, imaging and neurocognitive results of the mTBI patients.

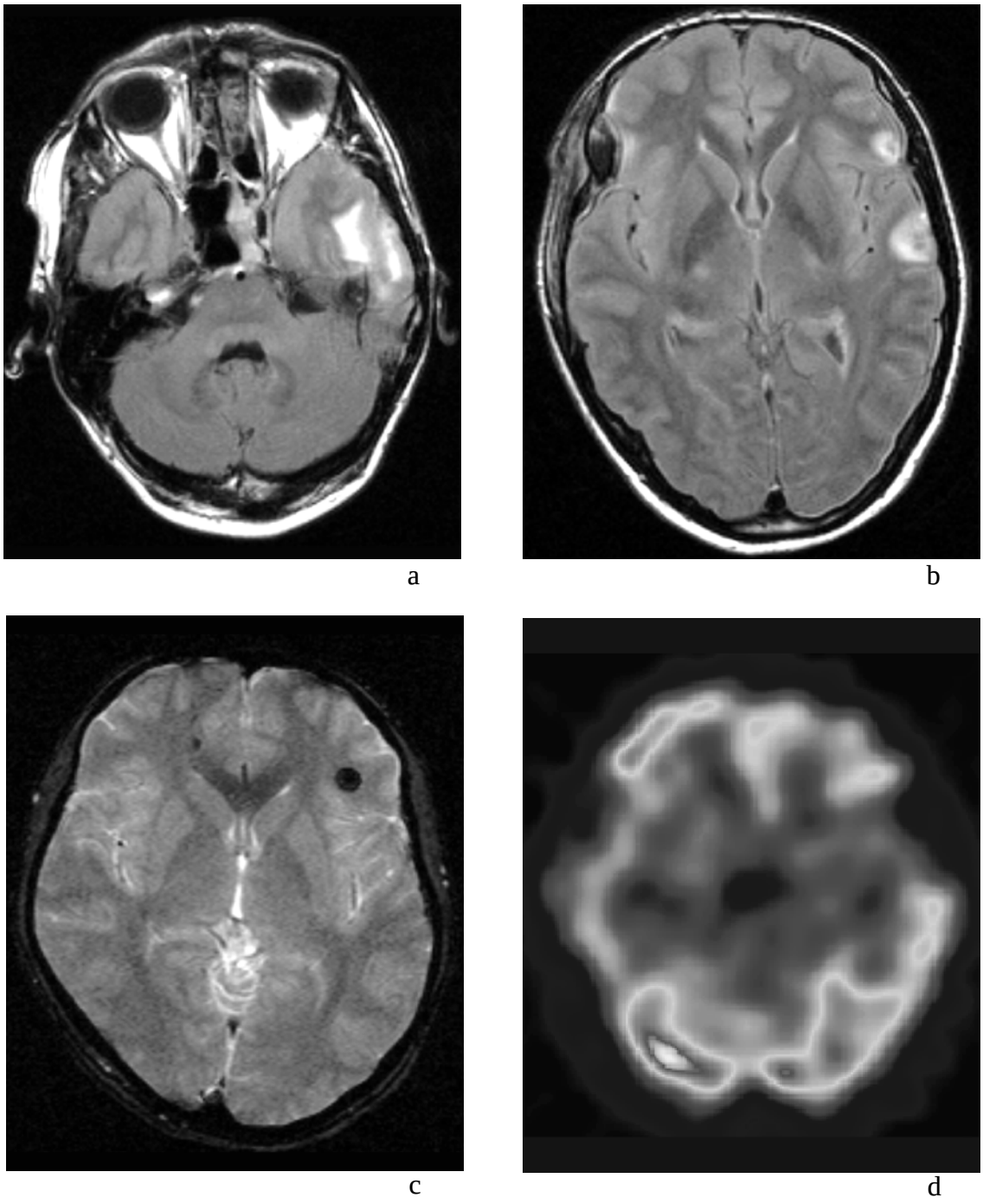

Figure 6.1: Mild traumatic brain injury. FLAIR images of a 36-years-old male who fell from a bicycle. Contusions are seen in the left temporal lobe as well as in the left frontal lobe. Note also the right frontal extra-cerebral haemorrhage (a & b). Two deep haemorrhagic lesions are seen on the T2- weighted image of a 23-year-old male who had a car accident (c). SPECT image of this patient shows a left frontal perfusion deficit (d), MRI showed no lesions at this location (not shown).*

No new lesions were detected at follow-up. There was a statistically significant reduction in

lesion volume on both the FLAIR images (mean 0.52 ml, SD 0.995 ml, p=0.02) and the FFE images (mean 0.50 ml, SD 0.84 ml, p=0.04). Patients with abnormal imaging study showed brain atrophy at follow-up, as expressed by a decreased tVBR. tVBR was significantly lower in patients with an abnormal MRI than in those with a normal MRI (normal: 1.04 (SD 0.03); abnormal: 0.94 (SD 0.08), student t-test, p=0.002). Division of the patients into two groups based on the SPECT findings also yielded the same difference in tVBR (normal: 1.04 (SD 0.02); abnormal 0.95 (SD 0.09), student t-test, p=0.03).

	normal MRI	abormal MRI	t-value	p-value
N	9	12		
age	22.8 (7.6)	22.8 (8.0)	0.04	NS
education level	5.0 (1.6)	5.1 (1.7)	-0.11	NS
years of education	13.8 (4.3)	13.3 (2.4)	0.30	NS
GCS score	14.6 (0.5)	14.4 (0.7)	0.70	NS
PTA	80 (96.9)	57.5 (75.4)	0.60	NS
LOC	4.4 (5.1)	3.7 (4.0)	0.36	NS

Table 6.2: Independent sample t-test on demographic variables and injury severity characteristics for patients with normal and abnormal MRI findings.

Neurocognitive examinations

A 22-year-old female was excluded from the analysis of the neurocognitive data because of a high probability of motivationally impaired performance.

The mean z-score for neurocognitive performance was -0.21 (SD 0.75) at the initial assessment, 0.14 (SD 0.60) after 2 months, and 0.45 (SD 0.52) after 6 months. This improvement was statistically significant for both intervals (MANOVA for repeated measurements $F(2,30)=12.711$, $p < 0.001$) (Figure 6.2). Patients with abnormal MRI had a lower z-score at initial assessment and after 2 months (Figure 6.2, Table 6.3). However, these differences were not statistically significant. Measures of cerebral damage (lesion volume and tVBR) did not correlate with the z-score of neurocognitive performance. The reaction time task (MCRT) after six months showed a difference between patients with abnormal and normal MRI findings. Patients with an abnormal MRI had a significantly slower reaction time on the incompatible reaction time task of the MCRT (t-test, $t(14)=-3.11$, $p=0.008$). There was no statistically significant difference between the number of symptoms scored on the questionnaire by patients with abnormal MRI and normal MRI findings (Table 6.4).

	NCE z-score acute	NCE z-score 2 months	NCE z-score 6 months
normal MRI	0.05 (0.53)	0.29 (0.39)	0.41 (0.54)
abnormal MRI	-0.37 (0.85)	0.05 (0.69)	0.47 (0.54)

Table 6.3: Mean z-score and standard deviation (between brackets) of the neurocognitive examination (NCE) of patients with normal and abnormal MRI.

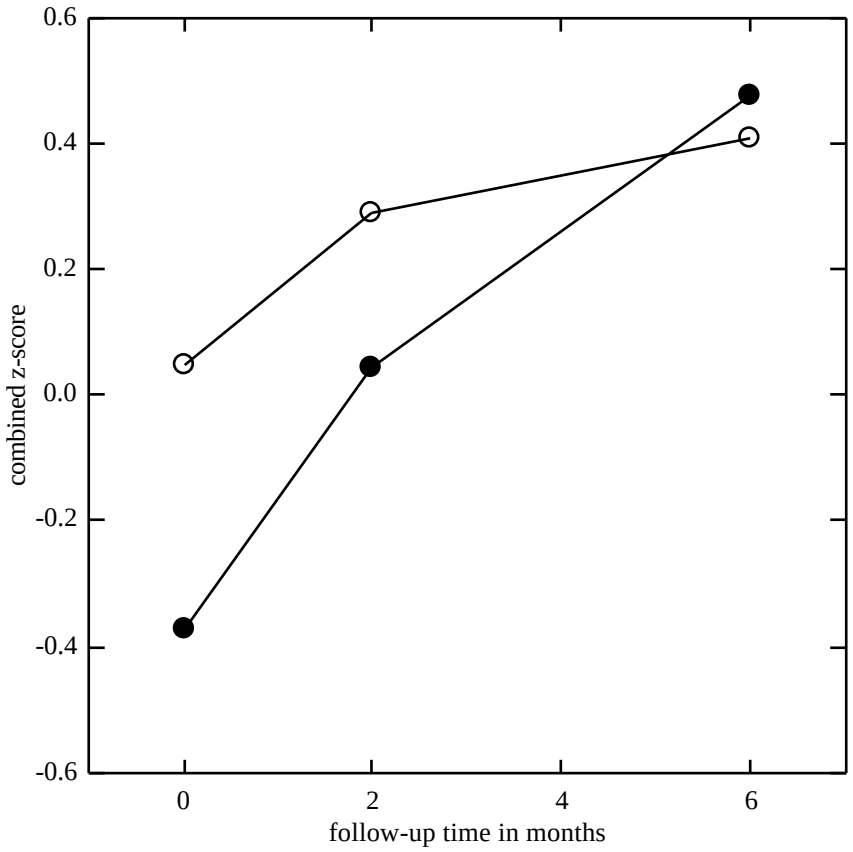

Figure 6.2: Combined z-scores of the patients with normal (○), and abnormal MRI findings (●) over the 6 months follow-up period.

Six months after injury, seven patients still had subjective cognitive complaints. Complaints of forgetfulness (39%) and difficulty in concentrating (33%) were the most common, followed by mild problems with word finding (28%) and mental slowness (22%). One patient complained

about difficulty in mental planning. One of the patients fulfilled the DSM-IV criteria of a post-concussional syndrome, and this patient had both an abnormal SPECT and abnormal MRI. There was no statistically significant association between SPECT findings and neuro-cognitive data.

	mean # of complaints at 2 months	mean # of complaints at 6 months
normal MRI	13.33	12.57
abnormal MRI	8.11	7.30

Table 6.4: Mean number of post-traumatic complaints as rated on a 28-item questionnaire.

Discussion

The present prospective study examined the prevalence of post-traumatic lesions in mTBI patients, using both MRI and HMPAO brain SPECT, and the relation between imaging findings and post-traumatic symptoms. This study is the largest reported prospective study of mTBI patients to use both neurocognitive investigations and neuroimaging. The most important finding in our series of mild traumatic brain injury patients was the high prevalence of brain lesions: 77% of the mTBI patients had either an abnormal MRI or an abnormal SPECT study. A recent meta-analysis has established the prevalence of haemorrhagic lesions in mTBI patients to be approximately 8%[32]. This estimation was based on CT findings. The prevalence of post-traumatic lesions may be somewhat higher, since not all lesions are haemorrhagic. Still, our findings show a relatively high sensitivity of MRI and SPECT for post-traumatic lesions. Patients with lesions on the initial MRI had brain atrophy at six months, as illustrated by the decrease in tVBR. This has also been shown in patients who sustained a moderate to severe head injury[33], but has not been reported previously in mTBI patients. These two findings illustrate that mTBI is accompanied by organic brain damage in a large percentage of patients. Cerebral perfusion changes detected on HMPAO SPECT reflect varying causes: areas with a clot show no perfusion, hypoperfusion can be caused by cerebrovascular effects of the injury, perfusion changes can be related to an uncoupling of metabolism and neuronal activity, which may lead to hyper- or hypoperfusion, and diaschisis may lead to hypoperfusion due to remote damage. SPECT is therefore sensitive to different types of change than MRI. This is corroborated by the low anatomical correlation between SPECT and MRI. However,

the characterization of an area of asymmetric activity as a lesion on a brain SPECT requires more fundamental knowledge of the relationship between brain pathology and brain SPECT. In the chronic, phase SPECT is considered more sensitive than CT and MRI[15-17]. However, in our series three patients had normal SPECT findings, while MRI revealed post-traumatic lesions. SPECT, on the other hand, showed post-traumatic alterations in four patients with a normal MRI.

The value of acute MRI in the management of head injury has not been determined. Previously, MRI was considered insensitive to early haemorrhage, which is the primary indication for neurosurgical intervention in head trauma patients, but new techniques have made MRI sensitive to acute haemorrhage as well. To date, however, CT is the modality of first choice to evaluate head trauma patients; it is more economical than MRI, easily accessible in most hospitals and simple to perform in agitated patients. Although we do not recommend the routine application of MRI in the management of mTBI, a wider application of MRI in mTBI patients seems justifiable, considering the superior sensitivity to post-traumatic brain lesions.

The heterogeneity of the head injured population,and the limited number of patients makes it difficult to demonstrate a relation between lesions and specific neurocognitive deficits. It is more feasible to demonstrate a correlation between measures that represent the overall severity of brain damage and general neurocognitive function[34]. We therefore combined the results of neurocognitive tests into a single z-score. In the acute phase and after 2 months patients with abnormal MRI study performed less well on neurocognitive testing. After six months these patients also performed less well on a reaction time task. These findings suggest an association between cerebral damage and neurocognitive performance. On the other hand, patients with a normal MRI tended to have more subjective symptoms. A larger prospective study is needed to elucidate this issue.

We did find a clear recovery of patients regarding neurocognitive measures as well as imaging findings. Although lesions were located most predominantly in the frontal and temporal lobes, the size and precise location differed considerably among patients. This heterogeneity is most probably due to differences in trauma mechanisms. The neurocognitive data also showed a heterogeneous image; different cognitive domains were more or less severely affected. It is likely that there is an association between the site of the lesions and the neurocognitive deficit. Levin et al showed an association between lesion location and performance on memory and planning tasks in a group of head injury patients[13]. The majority of patients in that series, however, had sustained moderate head injury. The heterogeneity of both organic lesions and neurocognitive deficits may explain why an association between these was not demonstrated. Another causative factor may be the age of patients.

At a mean age of 23 years, patients may have the cognitive flexibility to compensate for

small deficits. However, it has been suggested that biological life events, such as mTBI, could aggravate the effect of 'normal' cognitive aging[24, 28]. Considering the high prevalence of post-traumatic abnormalities, these patients could be at risk of earlier or more rapid cognitive decline when the normal biological aging process becomes evident. Furthermore, psychological and socioeconomic factors may also influence the recovery after mTBI.

Seven patients presented with persistent cognitive complaints, and one of these patients had a post-concussional syndrome according to DSM-IV criteria[3]. This prevalence of 5% is low relative to previously reported figures, which may be due to the age of the subjects as well. In a recent prospective study of mTBI patients, 25% had PCS at six months. In their control group of non-head injured patients, however, 34% of subjects also presented with complaints that met the PCS criteria[35]. Another study also found PCS-like complaints in 11% of patients not diagnosed with head injury[36].

Conclusion

The majority in a series of consecutive mTBI patients showed abnormalities on neuroimaging, and patients with abnormal neuroimaging findings had mild brain atrophy after 6 months. The correlation between MRI and SPECT results was poor, and more fundamental knowledge is needed to interpret brain perfusion SPECT studies. The neurocognitive performance of all subjects was within the normal range, and there was no difference in neurocognitive performance between patients with normal and abnormal MRI findings. Although our data suggest an association between MRI findings and neurocognitive performance, no significant association could be demonstrated. Other factors, such as the location of the lesions, psychological factors, age and educational level, might determine the outcome of mTBI at least as much as brain lesions.

Further research is needed to establish the relation between the apparent cerebral damage and its neurocognitive consequences, but a wider application of MRI in mTBI patients seems justifiable, considering the superior sensitivity to post-traumatic brain lesions.

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- CHAPTER 7 -

WHITE MATTER HYPERINTENSITIES IN NEUROPSYCHIATRIC DISEASE: INTRODUCTION AND METHODOLOGICAL CONSIDERATIONS

P.A.M. Hofman

Abstract

Since the introduction of MRI it has become clear that cerebral white matter hyperintensities (WMH) are often found on T2-weighted images of healthy subjects. However, the clinical implication of these hyperintensities has remained unclear. In addition several studies showed an association with neuropsychiatric disease. The next chapters describe a series of studies which were devised in order to gain insight in the pathophysiology of these disorders and the possible relevance of WMH in neuropsychiatric disorders. In this first chapter in this series is a general introduction with a methodological paragraph. Subsequently six studies are described on WMH in healthy volunteers, schizophrenia, bipolar mood disorders, Alzheimer's disease, cognitive decline, and alcohol-related disorders.

Introduction

MRI is a sensitive technique that permits the detection of subtle changes in the cerebral parenchyma. Because of the non-invasive nature of MRI, and because ionising radiation is not employed, it is extensively used to study populations of apparently healthy subjects.

Various investigators have reported a high prevalence of hyperintense areas in the cerebral white matter on T2-weighted images in such individuals. Previously, neurologically 'silent' white matter lesions had also been found on CT images of the brain. Hachinski et al[1] introduced the term 'leucoaraiosis' in the eighties to describe these white matter abnormalities seen on CT. The clinical significance of leucoaraiosis is limited, although they are associated with gait disturbances and a poorer outcome in stroke patients. Some reported an association with neurocognitive decline[2, 3], whereas others failed to document such a relation[4-6]. MRI is much more sensitive for detection of white matter abnormalities than CT[7, 8], and the prevalence of these hyperintensities on MRI is therefore much higher.

Three types of white matter hyperintensities (WMH) can be distinguished: dilated perivascular spaces or Virchow-Robin spaces (VRS); periventricular white matter hyperintensities (PVH); and subcortical white matter hyperintensities (SCH). The VRS is an extension of the extracellular space of the brain parenchyma[9]. VRS are mainly found in the cerebral white matter and basal ganglia, and rarely in the midbrain. VRS are not found in the pons or thalamus. The aetiology of VRS in unclear, but they may play a role in the clearance of extracellular fluid[10]. The patho-anatomical substrate of PVH is demyelination, and gliosis, and loss of ependymal lining[11]. This may occur because of leakage of CSF due to ependymal damage or augmented production of interstitial fluid[11, 12]. SCH are associated with arteriosclerosis, and the larger hyperintensities probably reflect ischaemic damage to the brain, with demyelination and gliosis as results[11]. Moody et al described periventricular venous collagenosis, a process associated with SCH[13]. PVH and SCH may have a different aetiology and patho-anatomical substrate. Most histopathological findings are done on brains showing hyperintensities in geriatric patients. However, histopathological data on 'asymptomatic' WMH in younger individuals are not available, and much is still unclear about the nature and aetiology of most WMH. Many authors report an increase in the prevalence of WMH with age[6, 14-20]. The association with cerebrovascular risk factors, such as hypertension[14, 18] and diabetes mellitus[15, 21-23], support at least a partial vascular aetiology of these hyperintensities.

Apart from applications in psychogeriatric and neurological disorders associated with aging, MRI is also used to study the cerebral changes in relation to neuropsychatric and psychiatric disorders in general. Various investigators have reported a higher prevalence of

WMH in patients suffering from various psychiatric conditions than in controls. This is of potential relevance because of the growing acknowledgement that a number of psychiatric conditions may in some way or another be determined by some type of brain dysfunction. WMH might be such a factor, not invariably producing a clear-cut cognitive or behavioural problem, but rather acting to increase vulnerability by hindering the information-processing ability of the brain[24]. Disruption of subcortical white matter tracts has been known to lead to loss of connectivity in the frontal-subcortical circuits and that this can induce behavioural changes is known since the early 20th century. Starkstein et al described mood disorders in stroke patients; depending on the location these could be manic or depressive in nature[25-27]. Subcortical dementia can also in part be caused by WMH[28, 29]. The size of the WMH reported in patients with neuropsychiatric disorders was much smaller than the hyperintensities described by Starkstein et al, and these hyperintensities were found not only in the prefrontal white matter. These smaller hyperintensities can be expected to lead to loss of connectivity and to a decrease in the speed of information processing. This has been demonstrated in mild head injury patients who perform less well on tests of divided and selective attention[30]. Diffuse axonal injury is found commonly in this category of patients[31]. It can be hypothesised that these WMH have a greater impact on post-traumatic outcome than grey matter lesions. More generally, WMH are assumed to increase the subjects' vulnerability and decrease the brain reserve capacity[32]. In subjects at risk for the development of neuropsychiatric disorders, it can be hypothesised that WMH increase their vulnerability and influence the expression of the disorder. It may even be the case that in some way these WMH represent a part of the biological basis for neuropsychiatric disorders.

To test the hypothesis of an association between WMH and neuropsychiatric diseases many studies have been performed in a variety of disorders. These studies have presented conflicting results with regard to the prevalence of white matter hyperintensities in normal and patient populations. A few important problems can be deducted from previous studies; the effects of population selection, data acquisition and rating techniques.

Population selection

The first is the issue of population selection: comparing a patient population with a control group recruited among health-care professionals or university personnel provides a great potential for bias. Since it has been suggested that subjects with a 'privileged background' are less susceptible for WMH[33], controlling for the socioeconomic status is mandatory. We used the final level of education as an approximation for socioeconomic status. The level of

education was measured on an 8 point scale, ranging from only primary school to an university degree[34]. In many studies it is assumed that age differences are controlled for by studying a large population with a wide age distribution. However, a strong correlation of WMH with age makes that studies with a smaller age range will have a greater statistical power, and possibly will reveal differences otherwise not found. There is a clear association between the WMH load and arterial blood pressure[14, 35]. Correlation with other cerebrovascular risk factors such as elevated triglyceride or cholesterol level is much more ambiguous. The history of a cerebrovascular accident is an important factor related to the prevalence of WMH[35]. It is therefore necessary to control for vascular risk factors as well as for age.

To test the association between neuropsychiatric disorders and white matter hyperintensities, these confounding conditions have to be controlled. Careful selection and matching of patient and control groups is mandatory.

Data acquisition

For the purpose of our study we defined WMH as those areas of white matter that have an increased signal intensity on both proton-density- and T2-weighted images (Figure 7.1). On T1-weighted images these hyperintensities are sometimes seen as hypointense areas. Different scan techniques have different sensitivities for the detection of WMH. The sensitivity of T1-weighted spin-echo images is comparable to that of CT for the detection of WMH. More strongly T1-weighted inversion recovery images have a higher sensitivity to WMH, but in practice the detection of WMH is almost exclusively performed with proton-density and T2-weighted images. Apart from the sequence parameters that determine image contrast, the geometric parameters also determine the sensitivity of a pulse sequence for the detection of WMH. There is a linear increase in observed hyperintensity with decreasing slice thickness because a thinner slice will result in the detection of smaller hyperintensities[36]. However, decrease in slice thickness will increase image noise. To compensate for this acquisition time can be increased, which however will increase motion artefacts, and degrade image quality. Most studies on WMH in neuropsychiatric disorders have employed a dual echo spin-echo pulse-sequence with a long repetition time, with early and late echoes, thus creating proton-density and T2-weighted images. Slice thickness varies between 5 and 10 mm with an interslice gap of 0 to 50%. Gradient-echo sequences are valuable for the detection of brain haemorrhage[37], and the short acquisition time makes these sequences useful in uncooperative patients. For the assessment of WMH, however, this sequence is of limited value due to poor signal-to-noise-ratio. Fluid attenuated inversion recovery (FLAIR) has the potential to replace spin-echo or turbo spin-echo sequences. FLAIR has proven to be more sensitive for the detection of white matter

hyperintensity in the supratentorial brain due to the higher white matter-WMH contrast. This improved conspicuity leads to a decrease in intra- and inter-observer variation[38]. However, FLAIR images have a lower signal-to-noise ratio than spin-echo or turbo spin-echo T2-weighted images and the sequence performs less well in the posterior fossa[39].

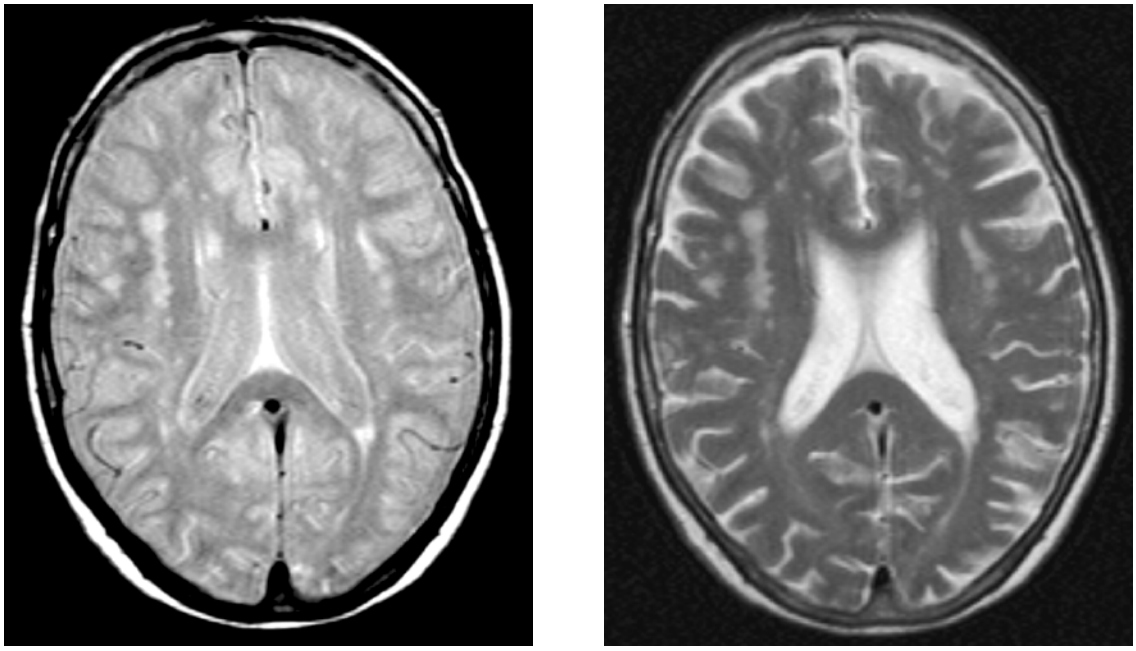
The MRI scans in this study were acquired on a 1.5 Tesla system (Philips Medical Systems, Best, The Netherlands). A T2-weighted turbo spin-echo sequence with two echoes (TR/TE 3000/23 and 120 msec, ETL 12) was used, with a slice thickness of 5 mm and an interslice gap of 10%. The field of view applied was 230 mm with a scan matrix of 187x256. A total of 24 slices were acquired in the transverse plane. The scans were evaluated on hardcopy. Scans with unacceptable artefacts were either repeated or excluded. All scans were performed in the University Hospital Maastricht.

White matter hyperintensity rating system

A rating system is a method to achieve data reduction; abnormalities are identified and a limited number of characteristics are recorded. Although many rating systems have been described and used in various studies there is no solid prior knowledge as to which features are most significant. A rating system should at least register information on the number, the size and the location of hyperintensities. A second important aspect is the practical applicability of the rating system. It should be easy to use, not too time-consuming, and reliable[40]. More or less dichotomous rating systems are easy to use, but little information on the hyperintensity characteristics is retained. Volumetric measurement of hyperintensities incorporating stereotactic information on the other hand is too time consuming. The rating scale described by Scheltens et al[41] meets many of the required demands. We therefore used this rating system with some modifications. By separating the metric assessment of the hyperintensities from the quantitative assessment we aimed at minimizing judgment errors and evaluation time, while retaining semi-quantitative information. Instead of the six severity scores used by Scheltens we used three classes of size and the number of hyperintensities. A further extension is the registration of the location of the hyperintensities in left or right hemisphere. This rating system has been used in a longitudinal population-based MRI study[42, 43], and was validated by Achten et al[44].

White matter hyperintensities were considered present if seen on both the proton-density and T2-weighted images. Dilated perivascular spaces and periventricular capping are considered normal by some[16, 45], and therefore not rated, whereas others found perivascular spaces to be associated with neurological disorders in children[46, 47]. We did not rate perivascular spaces. These hyperintensities are not seen on the proton-density image and this was used as the

criterium for exclusion.Subcortical white matter hyperintensities (SCH) (Figure 7.1) were scored separately from periventricular white matter hyperintensities (PVH). PVH were defined as those hyperintensities that extend from the lateral border of the cella media of the lateral ventricle (Figure 7.2). Periventricular hyperintensities were scored semi-quantitatively in three locations: adjacent to the frontal horn (frontal capping), adjacent to the cella media of the lateral ventricle (bands), and adjacent to the occipital horn (occipital capping). The scale ranged from 0 (normal) to 3 (large confluent hyperintensities). The overall degree of PVH load was determined by adding the three scores (range 0-9).



a b

Figure 7.1: Proton-density (a) and T2-weighted image (b) of a healthy subject with subcortical white matter hyperintensities.

The SCH were rated per region (frontal, temporal, parietal and occipital lobe, distinguishing left and right). The regions were defined in relation to cortical structures; frontal lobe - anterior to the central sulcus and superior to the Sylvian fissure; temporal lobe - inferior to the Sylvian fissure; parietal lobe -posterior to the central sulcus, and superior to the parieto-occipital sulcus; occipital lobe -inferior to the parieto-occipital sulcus. The basal ganglia, thalamus, and infratentorial brain were not incorporated in the anatomical rating. In a pilot study hyperintensities were very rarely found in these regions[38].

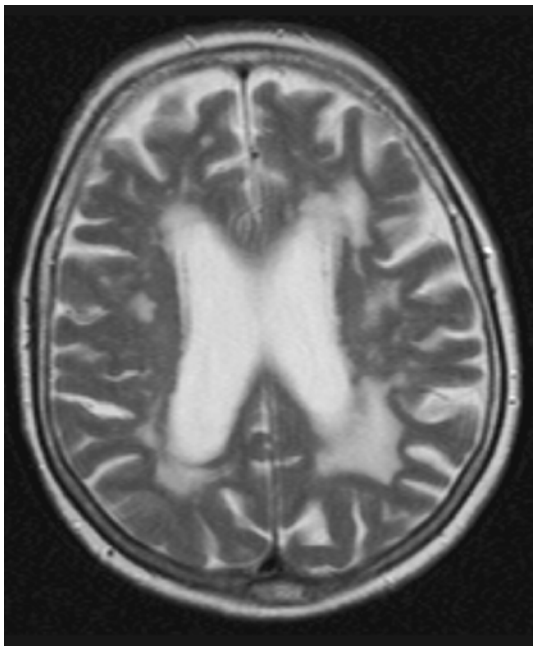


Figure 7.2: T2-weighted imege of a healthy subject with periventricular white matter hyperintensities

The number and size of the hyperintensities were recorded according to their largest diameter in three categories, small (<3mm), medium (3-10mm), and large (>10mm). In order to determine the total WMH load the number of hyperintensities in the three categories were added, after correction for size differences. Correction was achieved by multiplying the number of hyperintensities in each category by an estimated volume of the hyperintensities. All hyperintensities were considered to be spherical with a fixed volume per category (0.0042 ml, 0.18 ml, and 1.77 ml, respectively)[43]. The overall SCH load is expressed in a number that approximates the SCH volume. White matter hyperintensities of known aetiology (e.g. infarct, tumour) were recorded separately.

Since there is increasing evidence for a threshold effect of white matter hyperintensities with respect to their neurocognitive consequences[20, 48, 49], we used the quantitative data to identify subjects with large hyperintensities. The cut-off for large hyperintensities was set at the upper quartile of the distribution of WMH volume, in the population under study. Subsequently the prevalence of these larger hyperintensities was determined. This procedure was performed on the data of SCH and PVH separately.

We can distinguish several measures of WMH. The simple prevalence and the prevalence of large SCH and PVH, the approximate volume of SCH, and the 'raw' score of PVH (Figure 7.3). In the study on WMH in schizophrenic patients the simple prevalence and the prevalence of large periventricular bands are analysed separately. All data on WMH were analysed using nonparametric statistical procedures.

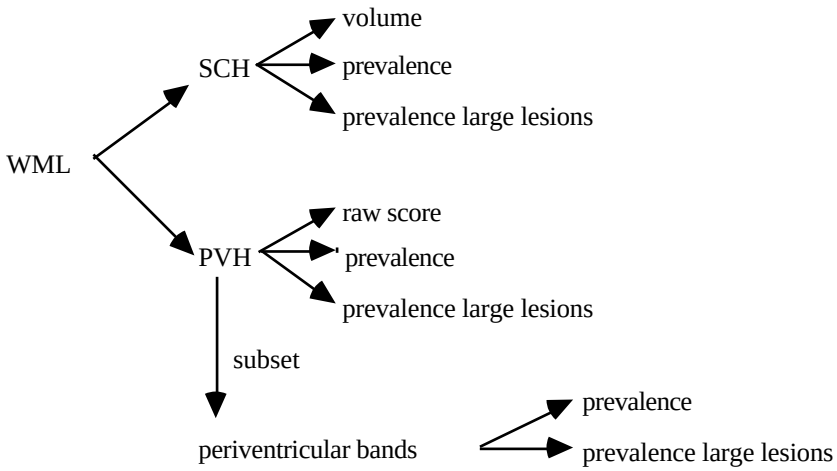


Figure 7.3: Schematic presentation of the different types of white matter lesions and their measures.

A hardcopy with pictorial references was used to maintain consistency through sessions. All MRI scans were read in twelve sessions, by an experienced neuroradiologist to determine the presence and extent of white matter hyperintensities. The rater was blinded for the diagnosis, age and sex of the subjects.
intra-observer reliability of this rating system was determined by double-reading the MRI scans of twenty-nine subjects. Inter-observer reliability was determined by double reading the MRI scans of another thirty patients by two experienced neuroradiologists.

The weighted kappa for the individual scores of PVH and periventricular bands were calculated, as well as the correlation coefficients of the total SCH[44]. The kappa values and correlation coefficients are given in Table 7.1. They show an adequate inter- and intra-observer reliability.

	intra-observer	inter-observer
	kappa	**kappa**
PVH	0.78	0.86
bands	0.83	0.79
	correlation	**correlation**
SCH	0.86*	0.90*

* $p < .0001$

Table 7.1: Intra- and inter-observer reliability expressed as the kappa and correlation coefficient.

Conclusion

Thus there is a need for a MRI study of WMH in a large population of patients suffering from a neuropsychiatric disease, using a well-selected normal control population. Care must be taken to match controls and patients, and to control for conditions that are known to be associated with WMH. In order to assess the influence of the rating scale, a semi-quantitative rating system, with anatomical subdivisions must be included. In order to be able to interpret the association between WMH and neuropsychiatric disorders it is mandatory to study the relation between WMH and age. This is the first aim of our study. The second goal is to assess the association between WMH and a few important neuropsychiatric disorders. Where appropriate, comparison will be made with previous studies and the implications will be discussed.

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- CHAPTER 8 -

WHITE MATTER HYPERINTENSITIES ARE COMMON IN HEALTHY ADULTS

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Abstract

Objectives-White matter hyperintensities are often found in healthy subjects. Most studies focused on the prevalence of white matter hyperintensities in the elderly population, and little is known about the prevalence of WMH in young healthy adults. White matter hyperintensities are of potential interest in neuropsychiatric disorders. The aim of this study is to establish the prevalence of WMH in a healthy population including young subjects.

Methods-Sixty-six healthy individuals aged 21 to 81 years were studied with MRI and white matter hyperintensities were rated using a semi-quantitative rating scale.

Results-There is a statistically significant correlation between the WMH load and age, in addition there is also a high prevalence of subcortical white matter hyperintensities in the young population (50%). Periventricular white matter hyperintensities appeared to be uncommon in the young population, and the prevalence increased significantly with increasing age.

Introduction

White matter hyperintensities are frequently found in healthy subjects without neurologic, psychiatric, or cognitive complaints[1]. These WMH are usually considered to be a random variation, and of little clinical consequence, although certain medical conditions are considered risk factors for the development of WMH[2-7]. The hyperintensities are attributed to vascular changes in the aging brain, but WMH can also be found in young individuals. There are several reasons why the prevalence of WMH in a healthy population needs to be determined. First, it is well established that the prevalence of WMH increases with age. Little is known however about the prevalence of WMH in the young population. Neuropsychiatric disorders can be found in the young individuals as well, especially bipolar mood disorder and schizophrenia. It is therefore important to gain insight into the prevalence of WMH in a population that includes young individuals. Secondly, available data are of limited value because few studies have rated PVH and SCH separately, and there are indications for a functional difference between these two types of WMH[8, 9]. It is thus of potential interest to rate these two types of WMH separately. Thirdly, different studies also applied different rating systems. The technical developments that have made MRI more sensitive in detecting WMH further limits the usefulness of older data.

The aim of this study is to establish the prevalence of WMH in a healthy population including young subjects. The rating system allows for the separate assessment of SCH and PVH. Conditions that could influence the incidence of WMH such as vascular risk factors and socioeconomic status are controlled for.

Subject and methods

Healthy individuals were recruited from the general population via newspaper advertisements. All subjects underwent a physical, a neurologic and a psychiatric examination. To control for conditions with a known association with WMH, subjects with neuropsychiatric disorders, cardiovascular disease, diabetes mellitus, hypertension, substance abuse in the last 12 months, and current psycho-active medication were excluded. Subjects with a history of head injury (unconsciousness over 1 hour) or with an excessive alcohol consumption (over 27 units a week) were also excluded. The study was approved by the medical ethics committee, and informed consent was obtained from all subjects. The subjects underwent a brain MRI study, and the proton-density and T2-weighted images were rated by an experienced neuroradiologist,

using a semi-quantitative rating system. Details of the image acquisition and the rating system are given in chapter 7. To study the effects of age, subjects were divided into three age groups; 20-45 years, 46-65 years and 66-81 years. The Chi square test was used to test for homogeneity of prevalence of WMH among the age groups. Subsequently the Mann-Whitney U test was used to analyse the difference among the groups. Difference in hyperintensity volume between groups was tested with the Kruskal Wallis test. To assess a possible threshold effect of WMH, the SCH data were dichotomised, with the cut-off point at the upper quartile of the distribution of SCH volume, as described in chapter 7. The same procedure was also applied to the PVH data. In this way five measures of WMH were assessed: the volume of SCH, the prevalence of all SCH and PVH, and the prevalence of both large SCH and PVH.

Results

Sixty-six healthy individuals were included in this study (38 males and 28 females). The mean age was 55 years (range 21-81 years). There was no statistically significant difference between the mean age of males and females (55 years and 54 years, t-test, p=0.78). Sex had no effect on the prevalence of white matter hyperintensities (Chi-square test, SCH p=0.48, PVH p=0.93). There was no difference in the volume of SCH between the left and right hemisphere (Wilcoxon Signed-Ranks Test, p=0.16). The frontal lobe had the highest volume of SCH, with a mean hyperintensity volume of 0.44 ml. The hyperintensity volumes of the other lobes are given in Table 8.1. There was a statistically significant correlation between the hyperintensity volume and age (Spearman rank correlation: SCH corr. coeff. 0.42, $p < 0.001$, PVH corr. coeff. 0.74, $p < 0.001$). There was no statistically significant correlation between the level of education and WMH volume (Spearman rank correlation: SCH corr. coeff. 0.05, p=0.7, PVH corr. coeff. -0.01, p=0.95).

	mean	25% perc.	50% perc.	75% perc.	95% perc.
frontal	0.44 ml	0	0.006	0.078	1.85
parietal	0.03 ml	0	0	0.004	0.22
temporal	0.03 ml	0	0	0	0
occipital	0.00 ml	0	0	0	0

Table 8.1: The volume of white matter hyperintensities in the four cerebral lobes, rated in a group of sixty-six healthy subjects.

The distribution of subjects among the three age groups was as follows: N=20 for the age group 20-45 years, N=23 for the age group 46-65 years and N=23 for the age group 66-81 years. There was a statistically significant positive effect of age on the volume of PVH (Kruskal-Wallis test test, $p < 0.0001$). The prevalence of all PVH as well as the prevalence of large PVH were different among the three age groups (Chi square test, $p < 0.0001$) (Table 8.2). The mean volume of SCH for the three age groups was 0.07 ml, 0.16 ml, and 1.21 ml, respectively. This difference was statistically significant (Kruskal-Wallis test, p=0.01). The prevalence of SCH increased with age, but this difference was not statistically different among the three age groups (Chi square test, p=0.08), however. The prevalence of large SCH showed a statistically significant difference among the age groups (Chi square test, p=0.02).

	N	SCH prev.	PVH prev.	large SCH	large PVH
I 20-45 years	20	50.0%	5%[a]	20%	0%[a]
II 46-65 years	23	65.2%	17%[b]	8.7%[b]	4.3%[b]
III 66-90 years	23	82.6%	82.6%	43.5%	56.5%

[a] significant difference between group I and III
[b] significant difference between group II and III

Table 8.2: Prevalence of all and large PVH and SCH in three age groups of healthy subjects.

The PVH had a prevalence of 5% in the youngest group and 82.6% in the eldest group. The prevalence of SCH was 50% in the youngest; 65.2% in the middle aged group, and 82.6% in the eldest group. Dichotomizing the data at the upper quartile results in a prevalence of 20% for SCH and 0% for PVH in the youngest group. In the eldest groups these prevalences were 43.5% and 56.5%, respectively.

Discussion

The most striking finding is the high prevalence of SCH in the youngest age group. The prevalence of 50% has not been reported previously. The prevalence of SCH in the oldest age group is also relatively high (83%). A possible explanation for this high prevalence is subject selection. This is of importance, as an association between socioeconomic status and the prevalence of WMH has been suggested[10]. The present study has recruited the subjects from the general population, instead of from scientific personnel. In contrast, in three studies where subjects were recruited from hospital staff[11, 12] or from other privileged subjects[13], the prevalence

of WMH in the young age group ranged from 0% to 6%. The single study in which controls were recruited from the general population showed a prevalence of WMH in the young group of 40%[14]. If the hyperintensity volume is considered instead of the prevalence of SCH, the difference between the three age groups becomes statistically significant. In other words, the rating system is very sensitive, and the prevalence data alone do not reflect the extent of white matter involvement completely.

The prevalence of PVH shows a more pronounced effect of aging: in the youngest age group only one subject had PVH, with increasing age this number increased dramatically. This again stresses the need for careful matching of patients and controls. Although education did not correlate with the prevalence of white matter hyperintensities, matching for education will improve the study design, because the level of education is an estimate for socioeconomic status. The effect of age on PVH and SCH is interesting because there seems to be a functional difference between the two. Interestingly, the prevalence of PVH has been found to be associated with diminished cognitive function, whereas the prevalence of SCH is associated with depression[8]. Cognitive decline is very prevalent in the elderly, and certain mood disorders (e.g. dysthymia) are also more common in the elderly population. The high hyperintensity volume of SCH in the elder population could be a biological basis for this phenomenon.

In conclusion, SCH showed a high prevalence in all age groups, but there was a statistically significant increase of hyperintensity volume with age. PVH were predominantly found in the elder population.

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- CHAPTER 9 -

SCHIZOPHRENIC PATIENTS ARE CHARACTERIZED BY WHITE MATTER HYPERINTENSITIES, A CONTROLLED STUDY

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Abstract

Objectives-The focus in schizophrenia research has long been directed towards grey matter abnormalities and little research has been performed on the white matter. However, white matter hyperintensities may also be aetiologically associated with schizophrenia. For example, periventricular white matter hyperintensities have been associated with perinatal asphyxia, which is also a known risk factor for schizophrenia. The aim of the present study is to assess the association between WMH and schizophrenia in a group of patients and matched control subjects.

Methods-Twenty-two schizophrenic patients (aged 31-57 years) and an equal number of controls (aged 21-57 years) were studied with T2-weighted MR images of the brain, and white matter hyperintensities were rated.

Results-The schizophrenic patients had significantly more periventricular bands than the control group. For the subcortical hyperintensities no difference between patients and controls were found.

Our results suggest that schizophrenic patients have a higher periventricular hyperintensity load than normal subjects. This is consistent with the hypothesis of a perinatal aetiology of schizophrenia.

Introduction

The focus in schizophrenia research has long been directed towards grey matter abnormalities and little research has been performed on white matter hyperintensities. However, white matter hyperintensities may also be aetiologically associated with schizophrenia. A disturbance in the frontal-striatal-thalamic circuitry has been proposed as an aetiological factor for schizophrenia. This concept has been based primarily on indirect evidence from psychopharmacology and analogies with animal research[1, 2]. It is known that subcortical white matter hyperintensities (SCH) can lead to loss of connectivity, and WMH can therefore present a part of the biological basis of schizophrenia. More in general, WMH may lead to an increased vulnerability of subjects by decreasing the brain reserve capacity[3], and reducing information processing efficiency[4]. This will make an individual more susceptible for environmental stress, especially in subjects predisposed to psychosis. Several studies reported an increased prevalence of WMH in bipolar patients[5], but only one study showed an increased prevalence in schizophrenics[6]. The significance of these findings remains unresolved, since other investigators did not show an association between schizophrenia and WMH[7, 8].

The aetiology of WMH in especially the young population is unknown, but a possible explanation for WMH in this population could be peri- or prenatal hypoxic or hypotensive events. These events have also been associated with an increased risk of schizophrenia[9-11]. The association of WMH and age is well established as is the association with vascular risk factors[12]. In order to be able to assess possible differences in prevalence of WMH between patients and controls, it is important to control for conditions with a known association with WMH. There are indications for aetiological difference between SCH and PVH[13, 14]. Furthermore, SCH and PVH appear to have different functional consequences: SCH have been associated with mood disorders, and PVH with cognitive decline[15]. In addition, PVH are associated with perinatal asphyxia[16], a known risk factor for schizophrenia. It is therefore mandatory to rate these two types of WMH separately.

Considering the potential contribution of WMH in the aetiology of schizophrenia, and the limited research performed in this field we set out to study the possible association between WMH and schizophrenia in a group of patients and matched control subjects, using a semi-quantitative rating scale, and we separately assessed SCH and PVH. We hypothesise that schizophrenic patients have a higher prevalence of WMH.

Subjects and methods

The schizophrenic patients were recruited from the local psychiatric departments (University Hospital Maastricht, RIAGG Maastricht and Psychomedical Centre Vijverdal Maastricht). At the time of assessment none of the patients was admitted. The diagnosis was made by a psychiatrist according to the DSM-IV criteria[17] and verified by means of the Composite International Diagnostic Interview[18]. Patients with schizo-affective disorders, left-handedness, history of head injury, cardiovascular disease, diabetes mellitus, hypertension, and substance abuse in the last 12 months were excluded. Patients over 60 years were not included. The controls were recruited via newspaper advertisements. Additional exclusion criteria for the control group were a history of psychiatric disease or the use of psycho-active medication. Patients and controls were matched for educational level, age and sex. The study was approved by the medical ethics committee, and informed consent was obtained from all subjects. Subjects underwent a brain MRI study, and the proton-density and T2-weighted images were rated by an experienced neuroradiologist, using a semi-quantitative rating system. Details on the image acquisition and the rating system are given in chapter 7. Since periventricular caps are considered normal by some[19, 20], the prevalence of periventricular bands was analysed separately**.** The Chi-square test was used to test for homogeneity of prevalence of WMH among patients and controls. To assess a possible threshold effect, the SCH data were dichotomised, with the cut-off point at the upper quartile of the distribution of SCH volume. The same procedure was also applied to the data of PVH and periventricular bands. In this way, eight measures of WMH were assessed. The prevalence of all and the prevalence of large SCH, PVH, and bands. For the analysis of the effect of age the volume of SCH and the 'raw' PVH data were used.

Results

Twenty-two schizophrenic patients and an equal number of controls were included. There was no difference in the level of education between patients and controls (Mann-Whitney U test p=0.96). The mean age of the patients was 40 years (range 31-57 years,12 males and 10 females). The mean age of the controls was 42 years (range 21-57 years, 9 males and 13 females). The prevalence of SCH, PVH and bands are given in Table 9.1. The schizophrenic patients had statistically significantly more periventricular bands than the control group (18%

vs 0%, chi-square test, p=0.04). For PVH as a whole (both bands and caps) the difference approaches significance (p=0.08), which is also reflected in the odds ratio of 6.17 (95% CI 0.66 - 58.03). For the SCH no difference between patients and controls was found. There is no statistically significant difference in the SCH volume between the left and right hemisphere (Mann-Whitney test p=0.07).

To study the effect of age the groups were divided at the 50% age percentile (38 years). In the younger group there was no difference in the SCH hyperintensities volume, whereas the patients had more PVH, with this difference tending to significance (Mann-Whitney U test p=0.07). In the older group the difference in PVH load between patients and controls was much smaller.

	SCH prev.	PVH prev.	bands prev.	large SCH	large PVH	large bands
controls	54.5%	4.5%	0%	22.3%	4.5%	0%
schizophrenics	50%	22.7%	18.2%	18.2%	22.7%	18.2%
p value	NS	0.078	0.036	NS	0.079	0.036
odds ratio	0.83	6.17				

Table 9.1: Prevalence of all and large PVH and SCH in schizophrenic patients and healthy subjects.

Discussion

The most important finding of this analysis is the increased prevalence of PVH and specifically periventricular bands in schizophrenic patients. The high rate of PVH supports the hypothesis of perinatal brain damage in schizophrenic patients[9-11]. Baeziget et al[16] showed that a periventricular distribution of white matter hyperintensities is a common pattern of brain injury in perinatal asphyxia. This is also supported by the increased frequency of obstetric complications in schizophrenic patients[21, 22]. Honig et al showed that schizophrenics are more exposed to environmental stress[23], and an alternative explanation for the high prevalence of WMH could be that these hyperintensities are a result of environmental stress and an effect of lifestyle. However, if WMH are caused by a different lifestyle of schizophrenics it can be assumed that the difference between patients and controls increases with a longer exposure to these environmental factors. Our data have shown no difference between the older patients and controls, and thus this alternative hypothesis of the aetiology of WMH seems less probable. Brown et al found no differences between controls and schizophrenic patients, but in that study PVH

were excluded from analysis. Bartzokis et al[8] were the first to consider both size and number of WMH in schizophrenic patients and controls, but they did not find a different prevalence in patients and controls. In that study, however, no distinction was made between PVH and SCH. Persaud et al[6] found a higher prevalence of SCH in schizophrenics, which is at variance with our results. However, in their definition, PVH did not have to be contiguous to the ventricular surface, meaning that a different separation was made between PVH and SCH. Another point is the scan technique applied. Instead of a dual spin-echo long-TR sequence, as we used, they applied a single echo technique with an image weighting between proton-density and T2, on a 0.5 Tesla scanner. This technique is less sensitive for detection of WMH, and will possibly reveal a subset of the hyperintensities found in our population. More detailed comparison of the results is not possible because prevalence data are not provided in the publication[6].

The higher prevalence of PVH in the young patients in our population, as opposed to the older patient group is in support of the vulnerability hypothesis. It can be hypothesised that increased prevalence of PVH in young schizophrenics represents a part the biological basis of their psychiatric disorder. This difference is seen to a lesser extent in the elder patient group, probably due to the blurring effect of aging, which yield higher prevalence numbers in the control group. The statistical power of our study is, however, not sufficient to allow a final conclusion.

In summary, our results suggest that schizophrenics have a higher periventricular hyperintensity load than normal subjects. A large scale replication using similar exclusion criteria is warranted to further verify these results.

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- CHAPTER 10 -

BIPOLAR MOOD DISORDER IS NOT CHARACTERIZED BY WHITE MATTER HYPERINTENSITIES: A CONTROLLED MRI STUDY

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Abstract

Objectives-White matter hyperintensities (WMH) may be associated with neuropsychiatric disorders. Various studies have reported high rates of WMH in patients with bipolar mood disorders, whereas other studies failed to show a different prevalence of WMH between patients and controls. Subject selection might explain these conflicting results. The purpose of this study is to evaluate the association between WMH and bipolar mood disorder in a group of patients and matched controls, controlled for known risk factors of WMH.

Methods-Twenty-two patients with a bipolar mood disorder (aged 34-58 years) and an equal number of controls (aged 32-58 years) were studied with a T2-weighted MRI of the brain, and white matter hyperintensities were rated.

Results-No statistically significant difference was found between the two groups.

It is suggested that the differences reported in the literature are partially based on a selection bias, and that in well controlled studies no increased prevalence of WMH is found in this patient group.

Introduction

White matter hyperintensities may be associated with neuropsychiatric disorders. Multiple sclerosis for example is related to depression and mania[1, 2]. Moreover, cerebrovascular accidents may lead to mood disorders in about 30% of cases[3], and there seems to be an association between the location of these cerebrovascular accidents and the nature of the mood disorder (manic or depressive)[4-6]. Cerebrovascular accidents occur mainly in the elderly population, while bipolar mood disorder is diagnosed in younger patients, and various studies have reported higher rates of WMH in patients with bipolar mood disorders[7-9]. These WMH may lead to an increased vulnerability of subjects by decreasing the brain reserve capacity[10], and make an individual more susceptible to environmental stress, especially in subjects predisposed to mood disorders. There is a clear association between these WMH and age as well as vascular risk factors[11, 12]. Such being the case it is interesting to note that other studies failed to show a statistically significant difference in the prevalence of WMH between patients and controls[13-15]. Subject selection can in principle explain these conflicting results very well. The aetiology of WMH in especially the young population remains unsolved, but a possible explanation for WMH in this population could be peri- or prenatal hypoxic or hypotensive events. In order to be able to assess possible differences in prevalence of WMH between patients and controls, it is mandatory to control for conditions with a known association with WMH, such as vascular risk factors. The purpose of this study is to evaluate the association between WMH and bipolar mood disorder in a group of patients and matched controls, rigorously controlled for known risk factors of WMH.

Subjects and methods

Patients with a bipolar mood disorder were recruited from the departments of psychiatry of the university hospitals of Maastricht and Utrecht. Controls were recruited from the general population. The diagnosis bipolar mood disorder was made by a psychiatrist according to the DSM-IV criteria[16] and verified by means of the Structured Clinical Interview for DSM-IV Disorders[17]. All patients had to be in remission for at least two months. Individuals with schizo-affective disorders, left-handedness, a history of head injury, cardiovascular disease, diabetes mellitus, hypertension, and substance abuse in the past 12 months were excluded. Patients over 60 years old were not included. The controls were recruited via newspaper advertisements. Patients and controls were matched for educational level, age and sex. Additional

exclusion criteria for the control group were a history of psychiatric disease or the use of psycho-active medication. The study was approved by the medical ethics committee of the University Hospital Maastricht, and informed consent was obtained from all subjects. The subjects underwent a brain MRI study at the University Hospital Maastricht, and the proton-density and T2-weighted images were rated by an experienced neuroradiologist, using a semi-quantitative rating system. Details on the image acquisition and the rating system are given in chapter 7. The Chi-square test was used to test for homogeneity of prevalence of WMH among patients and controls. To assess a possible threshold effect, the SCH data were dichotomized, with the cut-off point at the upper quartile of the distribution of SCH volume, as described in chapter 7. The same procedure was also applied to the PVH data. In this way four measures of WMH were assessed: the prevalence of all SCH and PVH, and the prevalence of large SCH and PVH. In order to be able to compare our results with data from the literature the odds ratios for the SCH and PVH were calculated as well.

Results

Twenty-two patients with a bipolar mood disorder and an equal number of controls were included. There was no difference in the level of education between patients and controls (Mann-Whitney U test p=0.40). The mean age of the patients was 47 years (range 34-60 years, 6 males and 16 females). The mean age of the controls was 47 years (range 32-58 years, 10 males and 12 females). The prevalence of PVH and SCH are given in Table 10.1. No statistically significant difference was found between the two groups, although patients tended to have more SCH as reflected by the odds ratio of 2.5 (95% CI 0.64 - 8.73). To study the effect of age the groups were divided on the 50% age percentile (47 years). There was no difference in prevalence of WMH between patients and controls in the two age groups.

	N	SCH prev.	PVH prev.	large SCH	large PVH
controls	22	59.1%	13.6%	22.7%	13.6%
bipolars	22	77.3%	13.6%	27.3%	13.6%
p value		NS	NS	NS	NS
odds ratio		2.35	1		

Table 10.1: Prevalence of all and large PVH and SCH in bipolar patients and healthy subjects.

Discussion

The hypothesis of an association of white matter hyperintensities and bipolar mood disorders is not supported by our data. However, the odds ratio does not allow outright rejection of the hypothesis either. A large number of studies have been published on the prevalence of white matter hyperintensities in bipolar patients, and a recent meta-analysis showed odds ratios ranging from 0.56 to 19[15]. Despite the differences, a test for heterogeneity of these odds ratios was not statistically significant[15], suggesting a relationship between cerebral white matter hyperintensities and bipolar mood disorders. Overall, WMH are found more frequently than expected in bipolar patients[15, 18]. The relatively high prevalence of SCH in our control group could explain why we did not find this difference. Ayward et al[9] for example found WMH in 3% of the controls, whereas Althshuler et al found WMH 40%. The prevalence of WMH in bipolar patients in these two studies were 59% and 66%, respectively. Therefore the selection of controls subjects is of importance. Ayward et al selected their controls among hospital staff and members of the surrounding community, whereas Althshuler et al recruited their controls from the general population. Another study showing an increased prevalence of WMH in bipolar patients also recruited hospital staff as control subjects[8]. Since it has been suggested that WMH are more likely to occur in people from a less privileged background[19], it is essential to control for this possible bias. We used the level of education as an approximation of socioeconomic status to match controls and patients. Our controls were recruited the from the general population. It seems therefore that the association reported previously between WMH and bipolar mood disorder is at least partially based on a selection bias in the control group.

In conclusion, our results show no significant differences between patients with a bipolar mood disorder and controls. It is suggested that the differences reported in the literature are partially based on a selection bias, and that in well-controlled studies no increased prevalence of WMH is found in this patient group. Further research is needed to assess the relation between socioeconomic status and the prevalence of WMH.

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- CHAPTER 11 -

PATIENTS WITH ALZHEIMER'S DISEASE DO NOT HAVE MORE WHITE MATTER HYPERINTENSITIES THAN MATCHED CONTROLS

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Abstract

Objectives-Many healthy subjects as well as patients suffering from non-vascular dementia have white matter hyperintensities (WMH), and these hyperintensities are also found in patients with Alzheimer's disease (AD). Further clarification of WMH in AD is important as it might give important clues to aetiology and risk-factors. Previous studies showed conflicting results with regard to the prevalence of WMH in AD patients. The aim of this study is to assess the association between WMH and AD, in a group of patients and matched control subjects. We carefully controlled for vascular risk factors and excluded patients with depression, since both conditions are associated with an increased prevalence of WMH.

Methods-Twenty eight AD patients (aged 56-85 years) and an equal number of controls (aged 56-81 years) were studied with a T2-weighted MRI of the brain, and WMH were rated.

Results-No statistically significant difference in prevalence of WMH was found between AD patients and healthy controls.

This finding supports the hypothesis that WMH in AD patients are related to aging and comorbid vascular factors, and are not an effect of AD as such.

Introduction

The neuropathologic hallmark of Alzheimer's disease (AD) is the deposition of amyloid ß-protein in neuropil and vascular walls and the formation of neurofibrillary tangles. This is accompanied by neuronal degeneration and atrophy of grey and white matter. The temporal lobe and the amygdala show the greatest vulnerability to these changes[1]. The functional outcome of this is dementia. On clinical grounds it is often difficult to distinguish between AD and vascular dementia. For the diagnosis of vascular dementia evidence of an infarct or extensive WMH is mandatory[2]. However, many healthy subjects as well as patients suffering from non-vascular dementia have WMH, and these hyperintensities are also found in AD patients. Further clarification of WMH in AD is important as it might give important clues to aetiology and risk-factors. Previous studies showed conflicting results with regard to the prevalence of WMH in AD patients (for a detailed description see the review by O'Brien et al[3]). In this study we aimed at assessing the association between WMH and AD in a group of patients and matched control subjects, using a semi-quantitative rating scale allowing for the separate assessment of SCH and PVH. We carefully controlled for vascular risk factors and excluded patients with depression, since both conditions are associated with an increased prevalence of WMH[4-8].

Subjects and methods

From the Maastricht Memory Clinic, an university based outpatient clinic and research facility for patients with cognitive impairment[9], subjects over 56 years were recruited. The diagnosis Dementia of Alzheimer's type was made by a neuropsychiatrist based on the DSM-IV[10] and NINCDS-ADRDA[11] criteria. Patients had a score over 14 on the Mini Mental State Examination[12] and a Global Deterioration Scale score[13] of 3,4 or 5. Patients with other neuropsychiatric disorders, or cognitive problems related to cerebrovascular events were excluded by means of the ischaemic score of Hachinski[14]. Head trauma, drug intoxication, alcohol abuse, hypo- or hyperthyroidism, and vitamin deficiency were additional exclusion criteria. The controls were recruited via newspaper advertisements, and patients and controls were matched for sex, age and educational level. Additional exclusion criteria for the control group included diabetes mellitus, clinical manifest cardiovascular disease (stroke, myocardial infarct, atrial fibrillation, vascular surgery) and hypertension. The study was approved by the medical ethics committee, and informed consent was obtained from all subjects. The subjects underwent a brain MRI

study, and the proton-density and T2-weighted images were rated by an experienced neuroradiologist, using a semi-quantitative rating system. Details on the image acquisition and the rating system are given in chapter 7. The Chi-square test was used to test for homogeneity of prevalence of WMH among patients and controls. To assess a possible threshold effect, the SCH data were dichotomised, with the cut-off point at the upper quartile of the distribution of SCH volume. The same procedure was also applied to the PVH data. This way four measures of WMH were assessed: the prevalence of all SCH and PVH, and the prevalence of large SCH and PVH.

Results

Twenty-eight AD patients and an equal number of controls were included. The mean age of the AD patients was 70 years (range 56-85 years, 12 males and 16 females). The mean age of the controls was 70 years (range 56-81 years, 12 males and 16 females). The level of education between patients a controls did not differ significantly (Mann-Whitney U test, p=0.35). The prevalence of PVH and SCH are given in Table 11.1. No statistically significant differences in prevalence of PVH and SCH were found between Alzheimer's patients and healthy controls. If the population is split into two age groups, 56-69 years (N=11) and 70-81 years (N=17), the prevalence of white matter hyperintensities in patients and controls remains equal, in both age groups.

	N	SCH prev.	PVH prev.	large SCH	large PVH
controls	28	82.1%	67.9%	17.9%	17.9%
Alzheimer	28	85.7%	71.4%	35.7%	25%
p value		NS	NS	NS	NS

Table 11.1: Prevalence of all and large PVH and SCH in Alzheimer patients and healthy subjects.

Discussion

It is an interesting finding that a group of AD patients, controlled for depression and vascular risk factors, did not show a statistically significant difference in the prevalence of both PVH and SCH compared to a group of matched controls. This is in contradiction with previous

studies that showed either a higher prevalence of SCH[15, 16] or of PVH[6, 17]. Those studies in which patients with vascular risk factors were excluded, however, failed to show an increased prevalence of white matter hyperintensities, which is in agreement with our results[18, 19]. While it can be argued that the prevalence of WMH in controls concealed differences between patients and controls, the prevalence of WMH in controls in the current study is in agreement with that found in other studies[20-26]. This supports the hypothesis that white matter hyperintensities in AD patients are related to aging and comorbid vascular factors, and not an effect of AD as such. The finding of pathological changes predominantly located in the cerebral grey matter supports this. The association of impaired cognitive function and white matter hyperintensities in AD patients, as shown by McDonalds[17] and Leys[27], does not refute this hypothesis, but merely suggests that the clinical presentation of AD depends on the coexistence of white matter hyperintensities.

In conclusion, our results show that patients with AD, carefully selected for the absence of depression and vascular risk factors, have a similar prevalence of SCH and PVH as matched controls.

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- CHAPTER 12 -

PATIENTS WITH COGNITIVE DECLINE, BUT WITHOUT DEMENTIA HAVE AN INCREASED PREVALENCE OF WHITE MATTER HYPERINTENSITIES

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Abstract

Objectives-Cerebral white matter hyperintensities (WMH) are commonly observed, and seem to be a part of the process of aging. The clinical consequences of WMH remain unclear. In the non-demented population, WMH have been associated with poorer neuropsychological test performances. The aim of this study is to assess the association between WMH and cognitive decline in a group of non-demented patients and control subjects.

Methods-Thirty-nine patient with cognitive decline but no dementia (aged 43-87 years), and an equal number of controls (aged 45-81 years) were studied with a T2-weighted MRI of the brain, and WMH were rated.

Results-Patients suffering from cognitive decline but no dementia had statistically significant more periventricular WMH than matched controls.

Introduction

Cerebral WMH occur with normal aging and are found more frequently in patients with hypertension and cerebrovascular disease. While WMH are commonly observed, our understanding of the clinical consequences continues to evolve. In non-demented patients with memory complaints, WMH have been associated with poorer neuropsychological test performances[1, 2]. The disruption of subcortical white matter tracts may reduce the speed of cognitive processes. This finding is of theoretical importance in view of the known cognitive slowness which evolves with age. The high prevalence of WMH in healthy individuals over 50 years suggests that these hyperintensities may also be a normal effect of aging. Individuals with cognitive complaints perform suboptimal on formal testing and many have a minor mood disorder (dysthymia)[3], but the prevalence of WMH in this mildly affected population is unknown. The prevalence of WMH in elderly patients with cognitive disorders is furthermore of interest because these symptoms might be a prodrome of dementia. A better understanding of the pathophysiology of this condition can give direction to intervention studies. Because there are indications for aetiological difference between SCH and PVH[4, 5], and SCH have been associated with mood disorders, and PVH with cognitive decline[2], it is of potential interest to assess both type of hyperintensities separately. The aim of the present study is to assess the association between WMH and cognitive decline in a group of patients and matched control subjects, using a semi-quantitative rating scale allowing for the separate assessment of SCH and PVH.

Subjects and methods

Subjects over 56 years were recruited for this study from the Maastricht Memory Clinic, an university based outpatient clinic and research facility for patients with cognitive impairment[6]. Patients were diagnosed with cognitive impairment no dementia (CIND) if they complained of cognitive impairment lasting for at least 6 months. Patients had Global Deterioration Scale score[7] of three or less. Patients with dementia or other neuropsychiatric degenerative disorders, patients with psychiatric disorders, or cognitive problems related to cerebrovascular events were excluded. A history of moderate to severe head trauma, drug or alcohol abuse, clinically manifest cardiovascular disease (stroke, myocardial infarct, vascular surgery), hypo- or hyperthyroidism, and vitamin deficiency were additional exclusion criteria. The controls were recruited via newspaper advertisements, and patients and controls were matched for sex, age

and educational level. Additional exclusion criteria for the control group included diabetes mellitus and hypertension. The study was approved by the medical ethics committee, and informed consent was obtained from all subjects. The subjects underwent a brain MRI study, and the proton-density and T2-weighted images were rated by an experienced neuroradiologist, using a semi-quantitative rating system. Details on the image acquisition and the rating system are given in chapter 7. The Chi-square test was used to test for homogeneity of prevalence of WMH among patients and controls. To assess a possible threshold effect, the SCH data were dichotomised, with the cut-off point at the upper quartile of the distribution of SCH volume. The same procedure was also applied to the PVH data. This way four measures of WMH were assessed: the prevalence of all SCH and PVH, and the prevalence of large SCH and PVH.

Results

Thirty-nine CIND patients and an equal number of controls were included. The mean age of the CIND subjects was 63 years (range 43-87 years, 23 males and 16 females). The mean age of the controls was 62 years (range 45-81 years, 23 males and 16 females). The level of education of CIND patients was slightly higher (median 3.5) than for controls (median 3). This difference, however, is not statistically significant (Mann-Whitney U test, p=0.09). The prevalence of PVH and SCH are given in Table 12.1. Patients suffering from CIND had statistically significant more PVH compared to matched controls (p=0.037). Patients also tended to have more large SCH as shown by the prevalence of SCH dichotomised at the upper quartile of the distribution. However, this difference is not statistically significant.

	N	SCLs prev.	PVLs prev.	large SCLs	large PVLs
controls	39	74.4%	48%	10.3%	7.7%
CIND	39	76.9%	71.8%	25.6%	12.8%
p value		NS	0.037	0.077	NS

Table 12.1: Prevalence of all and large PVHs and SCHs in patients diagnosed with cognitive decline no dementia (CIND) and healthy subjects.

Discussion

The main finding of this study is that subjects over 40 years old with cognitive impairment no dementia (CIND) have more PVH than matched controls. This supports the hypothesis of different functional consequences of PVH and SCH. De Groot et al[2] and Fukui et al[1] both showed that PVH are related to reduced cognitive functioning, the hallmark of CIND. Depression is associated with SCH[2], but the minor mood changes often found in CIND patients (dysthymia) are apparently not associated with SCH, as in our data the prevalence of SCH is the same in patients and controls. The prevalence of WMH in controls in the current study is in agreement with that reported in other studies[1, 8-13].

Interestingly we have found that Alzheimer's patients do not have a higher prevalence of WMH, whereas CIND patients do. This seems to contradict the assumption that CIND represents a prodrome of AD. However, CIND patients may constitute a heterogeneous group of different aetiologies (e.g. AD, vascular dementia), and it has to be considered that the CIND patients in our group are on average almost a decade younger than the AD patients presented in chapter 7. It can be hypothesised that the CIND patients develop PVH earlier and that these represent the larger PVH found in the AD patients. Our data, however, lack the statistical power to decide this issue.

In conclusion, our results show that patients with CIND without vascular risk factors have an increased prevalence of PVH compared to matched controls.

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- CHAPTER 13 -

WHITE MATTER CHANGES IN CHRONIC ALCOHOLISM AND KORSAKOFF'S SYNDROME: A CONTROLLED MRI STUDY

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Abstract

Objectives-Prolonged excessive alcohol consumption may lead to cerebral damage. Brain imaging research of alcohol related disorders has been focused on cerebral volume loss of predominantly grey matter and little is known about white matter hyperintensities (WMH) in these disorders. WMH are of interest because loss of connectivity between cortical and subcortical areas could aggravate the neurocognitive complains of patients. In the present study we compare the prevalence of WMH in a group of chronic alcoholics, patients with Korsakoff's syndrome and a control group.

Methods-Fourteen chronic alcoholics and fourteen patients with Korsakoff's syndrome were included, as well as an equal number of controls. All subjects underwent a T2-weighted MRI of the brain and the WMH were rated.

Results-In both patient groups the prevalence of WMH was significant higher than in the control group.

Introduction

Prolonged excessive alcohol consumption may lead to cerebral damage. There is still debate as to whether alcohol per se causes brain damage or that the damage is caused by other common alcohol-related factors, principally thiamin deficiency. There is volume loss of the brain in 'uncomplicated' alcoholics which can largely be accounted for by loss of both grey and white matter[1, 2]. Some of this volume loss appears to be reversible[3, 4]. However, alcohol-related neuronal loss has been documented in specific regions of the cerebral cortex due to the neurotoxicity of alcohol. The chronic amnestic disorder or Korsakoff's syndrome is found almost exclusively in chronic alcoholics, and caused by thiamine deficiency[5]. In these patients changes are found in the thalamus and mamillary bodies[6-8], as well as in the frontal lobe[2, 9].

Imaging studies of these two alcohol related disorders have focused on cerebral volume loss of predominantly grey matter and little is known about focal white matter hyperintensities in these disorders. Pfefferbaum et al[10] did not find an increased prevalence of WMH in chronic alcoholics, whereas Hayakawa et al[11] found an increased prevalence of both SCH and PVH. This last study however included subjects with cardiovascular risk factors and neurologic complications. No data are available on the prevalence of WMH in patients with Korsakoff's syndrome. WMH are of interest because it can be speculated that loss of connectivity between cortical and subcortical areas can aggravate the neurocognitive complaints of patients. In the present study we have compared the prevalence of WMH in a group of chronic alcoholics, patients with Korsakoff's syndrome and a control group. Conditions with a known association with WMH were controlled for by applying strict exclusion criteria. Groups were matched for age, sex and education.

Subjects and methods

Patients with an alcohol dependency (ADP) or Korsakoff's syndrome (KS) were recruited from the Vincent van Gogh Institute for Mental Health in Venray, The Netherlands. The diagnosis was made by a psychiatrist according to DSM-IV criteria[12]. The patients were abstinent from alcohol for at least one month. Patients with depression, dementia, diabetes mellitus, liver disease, CNS disorders and cardiovascular or pulmonary disorders were excluded. Only subjects younger than 56 years were eligible for inclusion in the study, because of the interaction between age and alcohol-related brain damage[10]. The controls were recruited via newspaper advertisements, and patient and control groups were matched for sex, age and

educational level. Additional exclusion criteria for the control group were a history of psychiatric disease or the use of psycho-active medication. The study was approved by the medical ethics committee, and informed consent was obtained from all subjects. The subjects underwent a brain MRI study, and the proton-density and T2-weighted images were rated by an experienced neuroradiologist, using a semi-quantitative rating system. Details on the image acquisition and the rating system are given in chapter 7**.** The Chi-square test was used to test for homogeneity of prevalence of WMH among the two patient groups and controls. Subsequently the Mann-Whitney U test was used to analyse the difference among the groups. To assess a possible threshold effect, the SCH data were dichotomised, with the cut-off point at the upper quartile of the distribution of SCH volume. The same procedure was also applied to the PVH data. This way four measures of WMH were assessed: the prevalence of all SCH and PVH, and the prevalence of large SCH and PVH.

Results

Fourteen ADP patients and fourteen KS patients were included, as well as an equal number of controls. The mean ages of the ADP and KS patients were 46 years (range 36-54 years) and 46 years (range 32-56 years) respectively. Both groups contained 11 males and 3 females. The controls had a mean age of 45 years (range 33-55 years, 12 males and 2 females). The level of education was not statistically significantly different among the three groups (Kruskal-Wallis test, p=0.2).

	N	SCH prev.	PVH prev.	large SCH	large PVH
controls	14	42.9%[b]	7.1%[a,b]	21.4%	0%a,b
ADP	14	57.1%[c]	71.4%	35.7%	28.6%
KS	14	92.9%	50%	21.4%	28.6%
p value		0.02	0.002	NS	NS

[a] significant difference between group controls and ADP
[b] significant difference between group controls and KS
[c] significant difference between group ADP and KS

Table 13.1: Prevalence of all and large PVH and SCH in patients with an alcohol dependency (ADP), Korsakoff's syndrome (KS), and healthy subjects.

The prevalence of PVH and SCH among the three groups was statistically significant and higher in the patients groups than in the control group (Chi square test SCH p=0.02, PVH p=0.002) (Table 13.1). KS patients have a higher prevalence of SCH and PVH than both ADP patients and controls. Both patient groups had a higher prevalence of PVH compared to the control group (Table 13.1). There is no difference in prevalence of PVH between the two patient groups. KS patients had more small SCH, illustrated by the fact that prevalence dichotomised at the upper quartile is equal to the prevalence of large SCH in the control group.

Discussion

Not many studies have been published on white matter hyperintensities in alcohol related disorders. Abnormalities in this population are thought to be caused by malnutrition, thiamine deficiency, and the alcohol toxicity. This gives rise to cerebral and cerebellar atrophy, most markedly in the diencephalon, the caudate nucleus, dorsolateral frontal and parietal cortex, and mesial temporal lobe structures of Korsakoff patients[1, 2]. The one study that reported an increased prevalence of WMH in ADP patients included subjects with medical and neurological disorders. We controlled for co-morbidity and excluded subjects with cardiovascular risk factors and psychiatric disorders. The higher prevalence of small SCH in KS patients is possible related to the thiamine deficiency, however, the prevalence of PVH shows a reversed trend with a higher prevalence in ADP patients. Therefore these findings need confirmation. A direction of further research could be the study of the association of WMH and patient or disease characteristics. This could elucidate the aetiology and functional consequences of WMH in these disorders. It can be hypothesised that WMH aggravate the functional consequences of neuronal loss in ADP and KS patients. In conclusion, in this controlled study we showed that detoxified ADP and KS patient have statistically significant more SCH and PVH than controls.

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- CHAPTER 14 -

WHITE MATTER HYPERINTENSITIES IN NEUROPSYCHIATRIC DISEASE: GENERAL DISCUSSION

P.A.M. Hofman

Soon after the introduction of MRI in clinical practice it was discovered that WMH are found in apparently healthy subjects. These hyperintensities were studied descriptively, and correlated to patho-anatomical specimens. This was the initial step in the understanding of the nature of WMH. The next logical step was to establish the possible correlation of these hyperintensities with clinical findings. Awad et al and Fazekas et al[1, 2] showed a correlation with age and cerebrovascular disease. In clinical practice, however, WMH were regarded as unidentified bright objects (UBO). While differentiating these UBOs from other hyperintensities, such as infarcts and MS plaques was important, the remaining hyperintensities however were considered of unclear clinical significance. The third step is to bring these remaining hyperintensities in the realm of brain-behaviour relations. This was the aim of the present study. The concept of increased vulnerability of subjects to cognitive decline due to the existence WMH is an important hypothesis in this context.

The present study is novel in that it comprises a relatively large group of subjects with various common neuropsychiatric disorders and matched controls. The second important feature is that subjects with conditions known to be associated with white matter hyperintensities were excluded. A third feature is the fact that two different anatomical categories of white matter hyperintensities were analysed separately, and that hyperintensity load is considered separate from prevalence, by also analysing the prevalence of larger hyperintensities.

We found that in a healthy population SCH are present in all age groups, but the total volume of the hyperintensities shows a statistically significant increase with age. PVH were found predominantly in the elder population. In schizophrenic subjects the prevalence of periventricular bands was increased. This increased prevalence of PVH was also found in elderly patients with age-related cognitive impairment. Subjects with Alzheimer's disease on the other hand showed no difference in prevalence of WMH compared to a group of matched controls. Finally, patients with alcohol related disorders showed an increased prevalence of both SCH and PVH.

Some methodological issues need attention. With regard to the rating system it is important to note that while all patient groups showed statistically significant more hyperintensities than matched controls, the significance depended on the choice of PVH or SCH and the cutoff (prevalence or upper quartile). This illustrates what is probably one of the main reasons for conflicting data from previous studies: different rating systems will give different results. Equally important is the threshold that is applied to decide which hyperintensities are considered normal and which are considered abnormal. The potential effect of threshold is increased by the improved MR image quality. The incomplete understanding of the pathogenesis and differences in the definition of its pathological features, makes it even more difficult to

interpret differences in prevalence of WMH. Large SCH are rated in all studies, but smaller hyperintensities not always, and the borderline between these two categories is not always clear. It is interesting to note that only in the study on normal aging was the volume of SCH significantly different between (age) groups. Both small periventricular caps and lines, as well as dilated perivascular spaces are often seen in normal individuals without neurologic or psychiatric signs or symptoms. Therefore these features can be considered effects of normal aging, and some do not classify them as white matter hyperintensities[3]. Small punctate hyperintensities may be widened perivascular spaces. Although considered as part of normal variance, these hyperintensities are associated with more severe white matter abnormalities. In a paediatric population, however, the existence of these perivascular spaces was associated with neurological and behavioural abnormalities[4, 5].

Our findings show the importance of distinguishing PVH from SCH which appear to have a different pathological correlate. PVH are associated with loss of ependymal lining, demyelination, and gliosis, which might result from periventricular water accumulation[6]. This may occur because of leakage due to ependymal damage or augmented production of interstitial fluid[6, 7]. SCH are associated with arteriosclerosis, and the larger hyperintensities probably reflect ischaemic damage to the brain, with demyelination and gliosis[6]. Moody et al described periventricular venous collagenosis, a process associated with SCH[8]. We showed the relevance of these small hyperintensities in patients with Korsakoff' syndrome. From a functional point of view PVH and SCH are presumed to be different as well. A quantitative EEG study showed a loss of coherence between areas connected by periventricular tracts in patients with PVH[9]. More research is needed to clarify both the aetiological and functional difference between different types of WMH.

Another important issue is subject selection. In order to asses the pathophysiological consequences of white matter hyperintensities in psychiatric disorders, confounding conditions such as cardiovascular risk factors (i.e. cardiovascular disease, diabetes mellitus) have to be excluded. This was done in the present study. In the same vein, including AD patients with depression is likely to result in an increased prevalence of SCH in the patient population, and such a selection bias should be prevented. The time between initial diagnosis and assessment of white matter hyperintensities is possibly of importance as well. It is very unlikely that a psychiatric condition is a direct consequence of white matter hyperintensities. Hyperintensities can be attributed to perinatal stress (e.g. in schizophrenics), or small vessel disease due to hypertension or diabetes mellitus. In either way these hyperintensities increase the vulnerability of the subject. A change in lifestyle, however, can aggravate the effect of aging on cerebral white matter. Homogeneity of the patient population with regard to disease duration is therefore desirable as well.

With regard to the MR acquisition technique a few remarks can be made. The sensitivity of MRI for the detection of white matter hyperintensities depends on the signal-to-noise ratio which is dependent upon the field strength of the magnet and the quality of the gradient system. Newer systems especially those with a higher field strength and new coil designs produce better signal-to-noise ratio. Comparing data from a low field scanner manufactured in the mid eighties, with data from a new high field scanner is difficult, especially when considering small hyperintensities. The acquisition parameters are of equal importance. Most previous studies used spin-echo T2-weighted sequences optimized for clinical imaging to evaluate the prevalence of white matter hyperintensities. Studies in MS patients, however, have shown that fluid attenuated inversion recovery images are more sensitive to white matter changes than spin-echo or turbo spin-echo proton-density and T2-weighted images. In line with this, the intra-rater and inter-rater reliability are higher when using these images[10]. Another advantage is that perivascular spaces are not well visualized on these images. Slice thickness is another matter of concern; thinner slices enable the detection of smaller hyperintensities. Older studies generally utilized 8 to 10 mm slices, while 5 mm slice thickness is presently the norm.

Conclusion and recommendations

Our data show that increased WMH are associated with cognitive decline in non-demented elderly patients. Alzheimer's disease however is not associated with increases in WMH. The findings in bipolar and schizophrenic patients are less conclusive, but the findings in the bipolar patients group stress the importance of careful selection of the control group. The high prevalence of WMH in alcohol-related disorders needs further study.

The conclusion can be drawn that WMH are associated with certain neuropsychiatric disorders. It would be interesting to study the mechanism of interaction between WMH and neurocognition. A multi-centre study, employing state-of-the-art imaging procedures, optimized for the automated assessment of WMH, and incorporating information on the localisation of WMH, could elucidate this issue in more detail. Other more innovative methods such as magnetisation transfer analysis[11], multi-component T2 analysis, and MR spectroscopy may give better in vivo characterisation of WMH. A next step could also be to study the functional consequence of WMH by means of functional MRI.

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- Chapter 15 -

CONCLUDING REMARKS

The central issues in this thesis are the nature of the possible relation between subtle structural brain lesions and neurocognitive and neuropsychiatric disorders, and the potential contribution of magnetic resonance imaging (MRI) in the evaluation of brain lesions. There is some evidence which supports the notion that subtle brain alterations are involved in the aetiology and pathogenesis of neuropsychiatric conditions. However, there are not many imaging studies which evaluate these conditions in depth. We have therefore studied two categories of subjects, namely patients who sustained a mild traumatic brain injury and patients who suffer from a neuropsychiatric disorder. Furthermore, the applicability of magnetisation transfer imaging for the assessment of cerebral white matter was explored. The most important implications of the findings which have been described in previous chapters will now be summarised in the following paragraphs.

Brain lesions in mild traumatic brain injury

Mild traumatic brain injury (mTBI) is generally considered a benign neurologic condition, from which most patients recover completely. However, some patients develop a persistent post-traumatic syndrome, consisting of neurocognitive deficits and a complex of symptoms. This may lead to profound psychological and professional problems, and patients may be handicapped by this post-concussional syndrome, with a serious reduction in the experienced quality of life. The main question in this thesis with regard to mTBI was therefore: is there an association between cerebral damage and neurocognitive deficits.

In the last decade, different imaging modalities have been used in the assessment of mTBI patients. Currently the plain skull X-ray is most widely used although it appears to be of little value. The main goal in acute imaging of head injury patients is to select those patients that need special care or neurosurgical intervention. The most threatening condition is that of an epidural haematoma, which may lead to a rapid deterioration of the patient, and which has, if untreated, a high mortality. The rationale behind the use of the skull X-ray is that it will detect those patients that are at risk for an intracranial haemorrhage. If a patient has a skull fracture, the chance that there is also an intracranial haemorrhage is increased with a factor 5. However, the majority of patients with an intracranial haemorrhage are not detected as they do not have a skull fracture. The sensitivity of the diagnosis of a skull fracture for the presence of an intracranial haemorrhage is 0.38, and the specificity is 0.95. Furthermore, intracranial haemorrhage has a prevalence of 0.083 in mTBI patients, which is much higher than reported previously. Therefore the plain skull X-ray is unsuitable for triage of mTBI patients.

In patients presenting with a Glasgow Coma Scale score of 15, without focal neurology,

no imaging is needed. For all other patients either observation or computed tomography (CT) is recommended. The implementation of these recommendations may have a profound impact on clinical practice, since the incidence of mTBI is in The Netherlands estimated at 0.14-0.64%. Although MRI is much more sensitive for traumatic lesions than CT, current clinical practice does not justify the routine application of MRI in the assessment of mTBI patients. However, this may change if neuroprotective drugs become available.

The superior sensitivity of MRI makes it a suitable modality to study the association between brain lesions and persistent post-concussional symptoms. Previously persistent neurocognitive complaints after a mTBI were considered a psychosomatic disorder. At this moment it is believed that the post-concussional syndrome (PCS) has a partial organic aetiology, although no brain imaging evidence existed for this assumption. We therefore studied a group of patients with a PCS after a mild or moderate head injury with neurocognitive tests and MRI of the brain including magnetisation transfer (see below). Patient results were compared with data from a matched control group. Patients performed significantly less well on neurocognitive testing compared to the control group, and they had significantly more white matter lesions. Histogram analysis of MTR data showed signs of brain injury. We therefore conclude that there is strong evidence of post-traumatic brain alterations in patients who sustained a relatively mild closed head injury, and that these results support the hypothesis of an at least partially organic aetiology for post-concussional symptoms in these patients.

Because retrospective studies have a strong potential for selection bias, it is very difficult to attribute brain lesions to the trauma. A longitudinal study is therefore needed to settle this issue. Such a study has been performed by us; in that study the presence of brain damage was determined with MRI and perfusion SPECT of the brain. Patients were included in the study immediately after the trauma. In the follow-up period neurocognitive tests were repeated at 2 and 6 months and MRI was repeated after 6 months. We found a high prevalence of cerebral lesions in these patients; 57% of the patients had post-traumatic lesions on MRI, and 61% had abnormalities on the SPECT study. Patients with abnormal neuroimaging showed mild brain atrophy after six months. Regrettably MTR data were not available for this patient group. The prevalence of post-traumatic lesions is much higher than the prevalence of intracranial haemorrhage of 0.083 as reported in chapter 3. This illustrates the high sensitivity of MRI and SPECT compared to CT. The neurocognitive performance of the patients appeared to be within the normal range. However, some qualitative indications have been found that patients with an abnormal MRI study do perform less well on a formal test immediately after the trauma and after two months. These differences were not statistically significant but they were in the expected direction. Additional studies with larger patient groups should be performed in order to evaluate this issue in more detail. After six months the performance of both groups is identical; only on a reaction time task patients with an abnormal MRI perform significantly

less. Of the twenty-one patients only one fulfilled the criteria of a post-concussional syndrome. We concluded that there is no statistically significant association between the results of subacute neuroimaging and neurocognitive performance, and that other factors, such as psychological factors, age and educational level, determine the outcome of mTBI at least as much as brain lesions.

The results of these studies illustrate the fact that mTBI is accompanied by brain lesions in a high percentage of patients, and that there is a possible association between lesions and neurocognitive performance. Furthermore it has been shown that patients with a post-concussional syndrome have more brain lesions than matched controls. It can therefore be concluded that it is very likely that there is an association between the existence of brain lesions and neurocognitive symptoms in mTBI patients. This relation between cerebral lesions and neurocognition is not straightforward, but the presented data do support the notion of an at least partial organic aetiology of neurocognitive deficits after mTBI.

It is notable that in the management of patients with orthopaedic injuries for instance, imaging and follow-up is used to identify high risk patients, and direct intervention. For some reason a trauma to a delicate organ as the brain does not justify the application of this model, and the use of sensitive imaging techniques is limited. This attitude hinders the progress in understanding the biological effects of mTBI, and the relation between these effects and their behavioural consequences. Wider application of MRI and larger prospective studies will further increase our knowledge, and may ultimately lead to a change in management of these patients.

White matter hyperintensities in neuropsychiatric disorders

White matter hyperintensities (WMH) are commonly found in neurologically and psychiatrically healthy subjects, but they are also seen in patients with neuropsychiatric disorders. Since the introduction of MRI many studies presented conflicting results with regard to the significance of WMH in neuropsychiatric disorders. This may be due to methodological differences and patient selection. The issue dealt with in this thesis is ‘how can these differences be explained and what is the significance of WMH in terms of association with various neuropsychiatric disorders’.

The exact aetiology of these white matter hyperintensities (WMH) is unknown, but they probably have a cerebrovascular cause. Three types of WMH can be distinguished, dilated perivascular hyperintensities or Virchow-Robin spaces (VRS), periventricular hyperintensities

(PVH) and subcortical white matter hyperintensities (SCH). VRS are commonly considered normal phenomena. PVH and SCH may have a different aetiology and different functional consequences and should therefore be considered separately. There are different ways in which WMH can be imaged and rated. Magnetic resonance imaging is by far the most sensitive method for the assessment of WMH, and a T2-weighted sequence is most commonly employed. There are considerable differences in rating systems, but a rating system should at least register information on the location, the size and the number of hyperintensities, and it should be easy to use, not too time-consuming, and reliable. We applied a semi-quantitative rating method that meets these criteria.

Because we are interested in the association of WMH and neuropsychiatric disorders, it is mandatory to control for conditions that have a known association with WMH. The first is age, but diabetes mellitus, hypertension, cerebrovascular disease, and head trauma are also associated with an increased prevalence of WMH. Since it has been suggested that subjects with a 'privileged background' are less susceptible for WMH, controlling for the socioeconomic status is mandatory as well.

In healthy subjects SCH were found in all age groups, but there was a statistically significant increase of hyperintensity volume with age. PVH were predominantly found in the elder population. Interestingly, the prevalence of PVH has been found to be associated with diminished cognitive function, whereas the prevalence of SCH is associated with depression. Cognitive decline is very prevalent in the elderly, and certain mood disorders (e.g. dysthymia) are also more common in the elderly population. The high volume of SCH in the elder population could be a biological basis for this phenomenon.

The prevalence of WMH in neuropsychiatric conditions differ, in a schizophrenic population an increased prevalence of periventricular bands was found. These bands and ventricular capping together form the PVH. On the other hand, in groups of patients with a bipolar mood disorder we found no increase in the prevalence of WMH compared with a control population. In the literature it is suggested that these patients have a higher prevalence of WMH, but these findings may, according to our results, be due to a selection bias of the control group. This stresses the need for careful matching of patients and controls. Patients with Alzheimer's disease were not different from controls with regard to the prevalence of WMH. Incidentally, it is important to note that patients with depression and vascular risk factors were excluded.

Non-demented patients with cognitive impairment had an increased prevalence of PVH compared with a matched control group. Both patients with Korsakoff's syndrome and alcohol dependent patients had more PVH and SCH.

The results of these six studies highlight that the selection of the patient and control group is extremely important as it may determine the outcome of the study. The second important point is that the rating system also determines which differences can be found. A rating

system that does not differentiate between PVH and SCH should not be used, and a semi-(quantitative) rating system enables a more subtle assessment of WMH.

The way these WMH contribute to neurocognitive disorders is not known, but it can be hypothesised that WMH lead to loss of connectivity and to a decrease in the speed of information processing. More generally, WMH may increase the subjects' vulnerability and decrease the brain reserve capacity. In subjects at risk for the development of neuropsychiatric disorders, WMH may increase their vulnerability and influence the expression of the disorder. It may even be the case that in some way these WMH present a part of the biological basis for neuropsychiatric disorders. However, not all neuropsychiatric disorders that were studied showed an association with the prevalence of WMH.

Magnetisation transfer imaging

Magnetisation transfer (MT) weighted imaging is a technique that allows for a quantitative assessment of tissue, and that is based on the principle of transfer of magnetisation from mobile protons, as in tissue water, to fixed protons, as in macromolecules. Because MT readily occurs in the adult cerebral white matter this technique is used to study cerebral changes, and it is generally assumed that a decreased MT ratio (MTR) is caused by a diminished macromolecular integrity. MT-weighted imaging has a potential application in group and longitudinal studies of white matter disorders. The transfer of magnetisation results in a decrease of signal intensity and the rate of MT is usually expressed as the MTR. However, MTR is typically measured in a region-of-interest (ROI), and the results depend on the position of the ROI. Another approach is to analyse the entire data set by presenting the MTR data as a histogram. This method introduces a bias because the MT data of both grey and white matter are analysed together and a change in grey/white ratio causes a change in the MTR histogram, that is unrelated to a change in the MTR.

An new post-processing technique is presented to circumvent this problem. Because of the potential application of this technique the effects of age and sex on white matter are of importance. Therefore the MT-weighted images of a group of healthy subjects were analysed. As to be expected there was an effect of age, with increasing age the mean MTR decreased, and the curve width increased. These effects are most likely due to increased water content and gliosis in combination with structural changes to the myelin. Surprisingly, we also found an effect of sex on the MTR of cerebral white matter. The mean MTR in females is lower than in males. The cause of this sex difference is not known, but it stresses the need to take also sex into account when interpreting MT-weighted imaging results.

This technique of MT imaging has the potential to replace 'conventional' imaging techniques

for the assessment of cerebral white matter. Because the method can be automated, inter- and intra-observer variations are not a major issue any more. An additional advantage is that the method can be standardized in such a way that results of different institutions can be combined, which makes the technique even more powerful. Future studies should aim at establishing the association between WMH and the MTR. Currently such a study is performed in our centre.

Conclusions

The data presented in this thesis highlight a few points. So called mild traumatic brain injury, is associated with high prevalence of brain lesions. The plain skull X-ray is unsuitable to select those patients with intracranial haemorrhage, but computed tomography also gives an underestimation of the actual damage to the brain.

White matter hyperintensities do occur in all age groups. Careful matching of patients and controls showed that the prevalence of these lesions is increased in schizophrenics, in elderly subjects with cognitive complaints and in alcohol related disorders. These findings are possibly of profound theoretical and clinical importance and therefore do need replication in a larger group or with a different technique. A promising technique is MT-weighted imaging; it is an operator independent method, and it proved to be sensitive to subtle white matter changes. A first step would be an analysis of the relationship between WMH volume and the MTR of white matter. To conclude, MRI bears promise of improving our insight into neuropsychiatric conditions which until recently have been considered to be mainly due to ‘psychological’ or ‘environmental’ factors.

SUMMARY

The central issues of this thesis are the nature of the relationship between structural brain lesions on the one hand, and neurocognitive and neuropsychiatric disorders on the other hand and the contribution neuroimaging can make in the evaluation of brain lesions. Two categories of subjects have been studied: patients who sustained a mild traumatic brain injury and patients who suffer from a neuropsychiatric disorder.

In chapter two the types of injuries found in patients who sustained a mild traumatic brain injury (mTBI) are described, as well as the different imaging modalities used in the assessment of these patients. The routine application of magnetic resonance imaging (MRI) in mTBI is not justifiable based on current clinical practice. Although MRI is more sensitive for traumatic brain lesions than computed tomography (CT), CT detects all lesions that determine the management of patients. The value of perfusion single-photon emission computed tomography (SPECT) is unclear, and this issue is addressed in chapter six. Currently the plain skull X-ray is still widely used. The main goal in acute imaging of mTBI patients is to select those patients who need special care, or neurosurgical intervention. The most threatening condition is that of an epidural haematoma, which may lead to a rapid deterioration of the patient, and which has, if untreated, a high mortality. The rationale behind the use of the skull X-ray is that it will detect those patients at risk for an intracranial haemorrhage.

In chapter three a meta-analysis is presented which only partly supports this assumption. If a patient has a skull fracture, the chance that there is also an intracranial haemorrhage is increased by a factor 5. However, the majority of patients with an intracranial haemorrhage will not be detected as they do not have a skull fracture. The sensitivity of the diagnosis of a skull fracture for the presence of an intracranial haemorrhage is 0.38, and the specificity is 0.95. Furthermore, intracranial haemorrhage has a prevalence of 0.083 in mTBI patients, which is much higher than reported previously. Therefore the plain skull X-ray is unsuitable for triage of mTBI patients. In patients presenting with a normal Glasgow Coma Scale score of 15, without focal neurology, no imaging is needed. For all other patients either observation or computed tomography (CT) is recommended.

Magnetization transfer (MT) weighted imaging is a technique that allows for a quantitative assessment of tissue. The transfer of magnetization results in a decrease of signal intensity and the rate of MT is usually expressed as the MT ratio (MTR). However, MTR is typically measured in a region-of-interest (ROI), and the results depend on the position of the ROI. Another approach is to analyse the entire data set by presenting the MTR data as a histogram. This method introduces a bias because the MT data of both grey and white matter are analysed together and a change in grey/white ratio causes a change in the MTR histogram, that is unrelated to a change in the MTR. In chapter four we therefore proposed a new

post-processing technique to circumvent this problem. White matter is segmented from CSF, grey matter and extra-cerebral tissue and subsequently the histogram of the white matter MTR distribution is analysed. To characterize this histogram we fitted a Gaussian function to the data, and thus the MTR histogram is characterized by the amplitude, the mean MTR and the curve width. This method is tested on a patient population with a post-concussional syndrome (PCS). This group was selected because the aetiology of PCS is still a matter of debate, and it is often considered a psychosomatic syndrome. If a new technique could show abnormalities in this group, it probably would do so in other conditions as well. The analysis of the segmented white matter is more sensitive for subtle white matter changes than the whole brain analysis. The new post-processing technique showed a significantly difference in curve widths between patients with a PCS and matched controls. Because of the potential application of this technique the effects of age and sex on white matter are of importance. Therefore the MT-weighted images of a group of healthy subjects were analysed. As to be expected there was an effect of age: with increasing age the mean MTR decreased, and the curve width increased. These effects are most likely due to increased water content and gliosis in combination with structural changes to the myelin.

Surprisingly, we also found an effect of sex on the MTR of cerebral white matter. The mean MTR in females is lower than in males. The cause of this sex difference is not known, but it stresses the need to take also sex into account when interpreting MT-weighted imaging results.

In chapter five brain damage in post-concussional syndrome (PCS) patients is studied. Previously persistent neurocognitive complaints after mTBI were considered a psychosomatic disorder. At this moment it is believed that PCS has a partially organic aetiology, although no imaging evidence exists for this assumption. We therefore studied a group of patients with a PCS after a mild or moderate head injury with neurocognitive tests and a MRI study of the brain. Patient results were compared with data from a matched control group. Patients performed significantly less well on neurocognitive testing compared to the control group, and they had significantly more white matter lesions. Histogram analysis of MTR data showed signs of brain abnormalities. We therefore concluded that this study provides strong evidence of post-traumatic brain alterations in patients who sustained a relatively mild closed head injury, and these results support the hypothesis of an at least partially organic aetiology for post-concussional symptoms in these patients. However, in a retrospective study there is a strong potential for selection bias, and it is very difficult to attribute brain lesions to the trauma. Therefore a longitudinal study was needed.

Chapter six describes such a study, where the association between neurocognitive perform-

ance and brain damage in mTBI is examined. The presence of brain damage was determined with MRI and perfusion SPECT of the brain. Patients were included in the study immediately after the trauma. In the follow-up period of six months neurocognitive tests and MRI were repeated. We found a high prevalence of cerebral lesions in these patients: 57% of the patients had post-traumatic lesions on MRI, and 61% had abnormalities on the SPECT study. Patients with abnormal neuroimaging showed mild brain atrophy after six months. The prevalence of post-traumatic lesions detected by MRI and SPECT is much higher than the prevalence of intracranial haemorrhage of 0.083 on CT as reported in chapter three. This illustrates the high sensitivity of MRI and SPECT compared to CT. The neurocognitive performance of the patients was within the normal range. However, patients with an abnormal MRI study performed less well on a formal test immediately after the trauma and after two months. These differences are not statistically significant. After six months the performance of both groups was identical, except for the performance on a reaction time task. Patients with an abnormal MRI perform significantly less well on this test. Of the twenty-one patients only one fulfilled the criteria of a PCS. We concluded that there is no significant association between the results of subacute neuroimaging and neurocognitive performance, and that other factors, such as psychological factors, age and educational level, determine the outcome of mTBI at least as much as brain lesions.

In chapter seven white matter changes are studied in a different way. Hyperintense regions may be found on the T2-weighted MR images of healthy subjects as well as on brain studies of patients with neuropsychiatric disorders. The exact aetiology of these white matter hyperintensities (WMH) is unknown, but they probably have a cerebrovascular origin. Three types of WMH are distinguished: perivascular hyperintensities or dilated Virchow-Robin spaces (VRS), periventricular hyperintensities (PVH) and subcortical white matter hyperintensities (SCH). VRS are commonly considered a normal phenomenon. PVH and SCH may have a different aetiology and should be considered separately. There are different ways in which WMH can be imaged and rated. Magnetic resonance imaging is by far the most sensitive method for the assessment of WMH, and a T2-weighted sequence is most commonly employed. There are considerable differences in rating systems, but a rating system should at least register information on the location, the size and the number of hyperintensities, and it should be easy to use, not too time-consuming, and reliable. We used a semi-quantitative rating method that meets these criteria. Because we are interested in the association of WMH and neuropsychiatric disorders, it is mandatory to control for conditions that have a known association with WMH. The first is age, but diabetes mellitus, hypertension, cerebrovascular disease, and head trauma are also associated with an increased prevalence of WMH. Since it has been suggested that subjects with a ‘privileged background’ are less susceptible for WMH, controlling for the socioeconomic

status is necessary as well.

In chapter eight the prevalence of WMH in a healthy population is described. SCH were found in all age groups, but there was a statistically significant increase of hyperintensity volume with age. PVH were predominantly found in the elder population. Interestingly, the prevalence of PVH has been found to be associated with diminished cognitive function, whereas the prevalence of SCH is associated with depression. Cognitive decline is very prevalent in the elderly as well as certain mood disorders (e.g. dysthymia). The high volume of SCH in the elderly population could indicate the biological basis for this phenomenon.

In a schizophrenic population presented in chapter nine an increased prevalence of periventricular bands was found. These bands and ventricular capping together form the PVH. This finding of an increased prevalence of periventricular bands supports a perinatal aetiology of schizophrenia.

In chapter ten we found no difference between patients with a bipolar mood disorder and a control population. In the literature it is suggested that patients have a higher prevalence of WMH, but these findings may, according to our results, be due to a selection bias of the control group. In some studies controls had a higher socioeconomic status than patients, and in those studies the prevalence of WMH in the controls was relatively low, enhancing the difference between patients and controls. This stresses the need for careful matching of patients and controls.

In chapter eleven we found that the prevalence of WMH in patients with Alzheimer's disease is not different from the prevalence in a normal population. In this study patients with depression and vascular risk factors were excluded.

In chapter twelve a non demented patient group with cognitive impairment is studied. In this group the prevalence of PVH is increased compared with a matched control group. In this comparison we also controlled for known risk factors of WMH.

A group of patients with alcohol related disorders was studied in chapter thirteen. Patients with Korsakoff's syndrome as well as alcohol dependent patients had more PVH and SCH. Further study is needed to determine the functional consequences of these WMH.

Chapter fourteen is a general discussion on WMH in neuropsychiatric disorders. For the concluding remarks and the conclusions of this thesis the reader is referred to chapter fifteen.

SAMENVATTING

De centrale thema's in dit proefschrift zijn de relatie tussen structurele hersenafwijkingen enerzijds en neurocognitieve en neuropsychiatrische afwijkingen anderzijds, en de bijdrage die beeldvorming kan leveren aan de beoordeling van deze afwijkingen. Twee groepen patiënten zijn hiervoor onderzocht: patiënten die een lichte hersenschudding (LH) hebben opgelopen en patiënten die lijden aan een neuropsychiatrische aandoening.

In hoofdstuk twee worden de verschillende soorten letsels beschreven zoals die gevonden worden bij patiënten die een LH hebben doorgemaakt. Tevens wordt een aantal beeldvormende technieken beschreven. Samenvattend kan worden gesteld dat na een LH hetzelfde type laesies wordt gevonden als na een zwaarder trauma, alleen zijn de laesies kleiner en geringer in aantal. Op basis van de klinische praktijk is het routinematig gebruik van magnetische resonantie beeldvorming (MRI) na een LH niet te rechtvaardigen. Alhoewel MRI gevoeliger is voor post-traumatische afwijkingen dan computer tomografie (CT), worden met behulp van CT alle voor de acute behandeling relevante laesies opgespoord.

De waarde van hersen single-photon emission computed tomography (SPECT) bij de beoordeling van patiënten met een LH is nog onduidelijk. In hoofstuk zes wordt hier verder op ingegaan.

Op dit moment is de conventionele schedelfoto een veel gebruikt beeldvormend onderzoek bij patiënten met een LH. Het belangijkste doel van de schedelfoto is om die patiënten te selecteren die verdere zorg behoeven. De meest bedreigende conditie is een epiduraal hematoom, hetgeen kan leiden tot snelle achteruitgang van de conditie van de patient. Onbehandeld kent het epiduraal hematoom een hoge mortaliteteit. De ratio van het gebruik van de schedelfoto is dat hiermee patiënten met een verhoogd risico voor een epiduraal hematoom worden opgespoord.

In hoofdstuk drie wordt een meta-analyse beschreven die bovenstaande aanname maar gedeeltelijk ondersteund. De aanwezigheid van een schedelfractuur verhoogt de kans op de aanwezigheid van een bloeding met een factor 5, echter, de meerderheid van de patiënten met een bloeding heeft geen fractuur. De sensitiviteit van de diagnose schedelfractuur voor de aanwezigheid van een intracraniële bloeding is 0,38 en de specificiteit 0,95. De prevalentie van deze bloedingen na een LH is 8,3%. Geconcludeerd wordt dat de schedelfoto ongeschikt is voor de triage van LH patiënten. Zij die een Glasgow Coma Scale score hebben van 15 (optimaal), en geen focale neurologische verschijnselen behoeven geen beeldvorming. Alle andere patiënten moeten of geobserveerd worden of onderzocht met behulp van CT.

Magnetisatie-overdracht gewogen MR beeldvorming is een techniek die het kwantitatief beoordelen van weefsel mogelijk maakt, met name van de cerebrale witte stof. De overdracht van magnetisatie resulteert uiteindelijk in een verlaging van het MR signaal en de mate van

deze afname kan worden uitgedrukt in een ratio, de “magnetisation transfer ratio” (MTR). De MTR kan lokaal berekend worden of over het gehele brein. Het gehele brein analyseren heeft het voordeel dat er gebruik wordt gemaakt van de hogere sensitiviteit van de methode. Het nadeel is dat het resultaat van deze analyse ook afhangt van de verhouding tussen de hoeveelheid grijze en witte stof. In hoofdstuk vier wordt daarom een alternatieve analysemethode beschreven. Omdat het primair om de witte stof gaat wordt deze gesegmenteerd en worden de grijze stof, liquor en andere extra-cerebrale structuren verwijderd. De MTR van de witte stof wordt vervolgens in een histogram gepresenteerd. Om dit histogram te karakteriseren wordt een Gausse curve gemodelleerd naar de MTR data en de hoogte en spreiding van de curve, en de positie van de piek karakteriseren het MTR histogram. Deze methode werd getest op MTR data van een groep patiënten met een postcommotioneel syndroom (PCS). Er werd voor deze groep gekozen omdat de etiologie van het PCS nog steeds onduidelijk is en PCS door velen beschouwd wordt als een psychosomatisch syndroom. Wanneer een nieuwe methode aanwijzingen aan het licht brengt voor een organische c.q. cerebrale oorzaak van PCS, dan zal deze methode waarschijnlijk ook afwijkingen laten zien bij andere aandoeningen. Het ligt voor de hand aan te nemen dat de analyse van gesegmenteerde witte stof gevoeliger is voor subtiele witte stof afwijkingen dan de analyse van het gehele brein, en deze aanname blijkt ook te kloppen. Omdat deze techniek goed gebruikt kan worden voor groepstudies werd ook gekeken naar de effecten van leeftijd en geslacht op het MTR histogram van de witte stof. Zoals verwacht daalt de gemiddelde MTR met het toenemen van de leeftijd en de wordt de curve breder. Deze effecten zijn het best te verklaren met een toegenomen watergehalte van de cerebrale witte stof, gecombineerd met gliose en structurele veranderingen van myeline. Er werd ook een verschil gevonden tussen mannen en vrouwen: de gemiddelde MTR is lager bij vrouwen. De oorzaak van dit sekseverschil is nog onduidelijk, het maakt wel duidelijk dat bij de beoordeling van MTR data ook het effect van het geslacht moet worden verdisconteerd.

In hoofdstuk vijf wordt verder ingegaan op hersenletsel bij PCS patiënten. Lang zijn persisterende neurocognitieve klachten na een mTBI gezien als psychosomatische. Thans wordt aangenomen dat PCS een deels organische etiologie heeft, al bestaan er nog geen studies die hersenletsel aantonen bij PCS patiënten. Daarom is een groep patiënten onderzocht met een PCS die meer dan een jaar eerder een LH hadden doorgemaakt. Zowel de patiëntengroep als een controlegroep werden onderzocht met neuropsychologische tests en een MRI van het brein. De patiënten presteerden duidelijk slechter bij het neuropsychologische onderzoek. Er werden ook meer witte stof afwijkingen gevonden bij de patiënten en ook de MTR histogram analyse liet een verschil zien tussen beide groepen. Deze studie verschaft dus sterke aanwijzingen voor post-traumatisch hersenafwijkingen bij patiënten met een PCS na een LH. Deze resultaten ondersteunden ook de hypothese van een organische etiologie van post-commotionele sympto-

men. Het nadeel van de retrospectieve opzet van de studie is echter dat er een grote kans is op een onbedoelde patiënten selectie. Een prospectieve studie is daarom noodzakelijk.

In hoofdstuk zes wordt zulk een studie beschreven. Patiënten met een LH werden direct onderzocht met behulp van een MRI, perfusie SPECT en neuropsychologisch onderzoek. Patiënten werden vervolgens nogmaals onderzocht na twee en na zes maanden. Er werd een hoog percentage patiënten gevonden met hersenletsel: bij 57% van de patiënten werden afwijkingen gezien op MRI en bij 61% op het SPECT onderzoek. Patiënten met afwijkingen hadden cerebrale atrofie op het onderzoek na zes maanden. De prevalentie van dergelijke post-traumatische afwijkingen is veel hoger dan de prevalentie van intracraniële hematomen van 8,3% die eerder werd gerapporteerd. Dit illustreert dat CT een onderschatting geeft van uitgebreidheid van de cerebrale schade na een LH. De patiënten presteerden binnen de normale spreiding op de neuropsychologische tests. Patiënten met een hersenletsel presteerden echter wel slechter direct na het trauma en na 2 maanden. Zes maanden na het trauma is er geen verschil meer tussen patiënten met en zonder hersenletsel. Alleen op een reactietijdtest presteerden patiënten met een hersenletsel slechter na 6 maanden. Van de 22 patiënten was er slechts één die voldeed aan de criteria van een PCS. Het lijkt er dus op dat er naast hersenletsel ook andere factoren een rol spelen bij de etiologie van het PCS. Daarbij kan gedacht worden aan psychologisch factoren, leeftijd en opleiding.

In hoofdstuk zeven wordt een ander aspect van cerebrale schade bestudeerd. Hyperintense gebieden worden zowel gevonden in de witte stof van gezonde personen als van patiënten met een neuropsychiatrische ziekte. De exacte etiologie van deze witte stof hyperintensiteiten (WMH) is onbekend, maar ze hebben waarschijnlijk een cerebrovasculaire oorzaak. Er kunnen drie type WMH worden onderscheiden, perivasculaire hyperintensiteiten of Virchow-Robin ruimtes (VRS), subcorticale witte stof hyperintensiteiten (SCH) en periventriculaire witte stof hyperintensiteiten (PVH). Over het algemeen worden VRS beschouwd als een normaal verschijnsel. PVH en SCH lijken een verschillende etiologie te hebben en moeten apart beoordeeld worden. Meestal worden WMH bestudeerd op T2-gewogen MR beelden. Er zijn verschillende visuele beoordelingsschalen, maar op z'n minst moet de plaats, het aantal, en de omvang worden genoteerd. Daarnaast moet de methode eenvoudig te gebruiken zijn, betrouwbaar en niet te arbeidsintensief. Wij gebruikten een semi-kwantitatieve scoringsmethode welke aan deze criteria voldeed. Omdat we geïnteresseerd zijn in de relatie tussen WMH en neuropsychiatrische ziekte is het van belang dat andere predisponerende factoren voor WMH worden gecontroleerd. Op de eerste plaats is dit leeftijd, maar ook diabetes mellitus, hypertensie, cerebrovasculaire afwijkingen en hersentrauma zijn geassocieerd met een toegenomen prevalentie van WMH. Ook is het nodig rekening te houden met de socioeconomische klasse van personen. In hoofdstuk acht wordt de prevalentie van WMH in een gezonde populatie beschreven.

SCH werden in alle leeftijdsgroepen gevonden, maar met het toenemen van de leeftijd is er een duidelijke toename. PVH werden met name gevonden in de oudere populatie. Dit is van belang omdat de prevalentie van PVH geassocieerd wordt met een achteruitgang van cognitieve functies en SCH worden geassocieerd met stemmingsstoornissen. Cognitieve achteruitgang komt veel voor op gevorderde leeftijd, en bepaalde stemmingsstoornissen hebben ook een hogere prevalentie in de oudere populatie. Het grotere volume van SCH in de oudere populatie is mogelijk een biologische basis van dit fenomeen.

In hoofdstuk negen wordt de prevalentie van WMH beschreven in een groep schizofrene patiënten. Vergeleken met een controlegroep is er bij de patiënten een verhoogde prevalentie van periventriculaire banden, een subset van de PVH. Deze bevinding ondersteunt de hypothese van een perinatale etiologie van schizofrenie.

In hoofdstuk tien worden geen verschillen gevonden in de prevalentie van WMH tussen een controlepopulatie en een groep van patiënten met een bipolaire stemmingsstoornis. In de literatuur wordt beschreven dat de prevalentie van WMH in deze patiëntengroep hoger is dan bij controles. Volgens onze resultaten kan dit verschil verklaard worden door verschillen in de controlepopulaties. In sommige studies hadden de controles een hogere socioeconomische status dan de patiënten, en juist in deze studies was er een groot verschil tussen patiënten en controles. Dit benadrukt nogmaals het belang van een zorgvuldig samengestelde controlegroep.

In hoofdstuk elf wordt beschreven dat de prevalentie van WMH bij patiënten met de ziekte van Alzheimer gelijk is aan die in de controlegroep. Patiënten met depressie en cardiovasculaire risico factoren werden uitgesloten van de studie.

In hoofdstuk twaalf wordt de prevalentie van WMH onderzocht in een groep patiënten met een verminderd cognitief functioneren. In deze groep worden meer PVH gevonden dan in de controlegroep.

In hoofdstuk dertien worden patiënten met het syndroom van Korsakoff en alcoholafhankelijkheid onderzocht. Ook deze twee patiëntengroepen worden vergeleken met een controlegroep. Beide patiëntengroepen lieten een verhoogde prevalentie zien van zowel PVH als SCH. Verdere studie is nodig om het functionele belang van deze WMH te bepalen.

In hoofstuk veertien wordt een algemenene discussie gepresenteerd over WMH bij neuropsychiatrische patiënten en over de gebruikte onderzoeksmethodologie.

De in dit proefschrift gepresenteerde resultaten benadrukken een aantal zaken. De zogenaamde lichte hersenschudding gaat gepaard met een hoge prevalentie van hersenletsel. De schedelfoto is een ongeschikte methode om uit deze groep de patiënten te selecteren met een intracranieel hematoom, maar ook de CT geeft een onderschatting van de cerebrale schade.

Witte stof afwijkingen worden gevonden in alle leeftijdsgroepen. Een zorgvuldige vergelijking tussen patiënten en een gezonde controlepopulatie laat zien dat de prevalentie verhoogd

is bij schizofrene patiënten, bij oudere personen met cognitieve klachten en bij patiënten met alcohol gerelateerde cerebrale afwijkingen. Deze bevindingen kunnen een belangrijke theoretische en klinische implicatie hebben en moeten daarom bevestigd worden in een grotere studie of in een studie met een andere techniek. Magnetisatie-overdracht gewogen beeldvorming is veelbelovend voor de kwantitatieve beoordeling van de cerebrale witte stof. Een logische volgende stap is de bepaling van de relatie tussen de MTR histogram analyse en de visuele WMH beoordeling.

Concluderend, het gebruik van MRI vergroot ons inzicht in de etiologie van neuropsychiatrische condities die tot voor kort voornamelijk verklaard werden met psychologische en omgevingsfactoren.

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Curriculum Vitae

Paul Hofman werd op 18 juni 1961 in Baak geboren. In 1979 deed hij eindexamen VWO aan het St. Ludger College te Doetinchem. De studie geneeskunde aan de Katholieke Universiteit Nijmegen werd in 1987 afgesloten met het arts-examen. Hierna werkte hij gedurende anderhalf jaar als arts-assistent op de afdeling Algemene Heelkunde van het St. Radboud Ziekenhuis te Nijmegen (Prof. dr. H.H. de Boer en Prof. dr. R.J.A. Goris). In 1989 startte hij met de opleiding tot radiololoog in het Academisch Ziekenhuis Maastricht (opleider Prof. dr. B. K. Janevski). Van 1995 tot 1999 was hij werkzaam als fellow en gedurende deze periode werd het onderzoek verricht dat leidde tot deze dissertatie. Sinds medio 1999 is hij als staf-radioloog verbonden aan de afdeling radiologie van het Academisch Ziekenhuis Maastricht.