Clinical and therapeutic aspects of Cerebral Palsy

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Clinical and therapeutic aspects of Cerebral Palsy

GEORGES VLES

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Clinical and therapeutic aspects of Cerebral Palsy

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus Prof. Mr. G.P.M.F. Mols,
volgens het besluit van het College van Decanen in het openbaar te verdedigen
op vrijdag 22 juni 2012 om 10:00 uur

door

Georges Vles

Geboren in 1986 te Maastricht

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To my parents

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LIST OF ABBREVIATIONS

AOC	Angle Of Catch
BBB	Blood Brain Barrier
BMI	Body Mass Index
BTX-A	Botulinum Toxin A
BTX-B	Botulinum Toxin B
CBCL	Child Behavior Checklist
CFA	Confirmatory Factor Analysis
CHQ	Child Health Questionnaire
CITB	Continuous Intrathecal Baclofen
CNS	Central Nervous System
CP	Cerebral Palsy
CS	Communication Skills
CT	Computed Tomography
DMD	Duchenne Muscular Dystrophy
DTI	Diffusion Tensor Imaging
EMG	Electromyography
GABA	Gamma-Aminobutyric Acid
GAS	Goal Attainment Scale
GMFM	Gross Motor Function Measurement
GMFCS	Gross Motor Function Classification System
ICF	International Classification of Functioning, disability and health
ITB	Intrathecal Baclofen
IQ	Intellectual Quotient
LAQ-CP	Lifestyle Assessment Questionnaire - CP
LEV	Levetiracetam
LoH	Level of Hand function
MUMC	Maastricht University Medical Centre
MAS	Modified Ashworth Scale
MRI	Magnetic Resonance Imaging
PARS-III	Psychosocial And Role Skill Scale - III
PEDI	Pediatric Evaluation of Disability Inventory
PPVT-III-NL	Peabody Picture Vocabulary Test - III - NL

PROM	Passive Range Of Motion
QoL	Quality of Life
RF-DRG	Radio Frequency lesion of the Dorsal Root Ganglion
ROC	Receiver Operating Characteristic
SCPE	Surveillance of Cerebral Palsy in Europe
SD	Standard Deviation
SDR	Selective Dorsal Rhizotomy
SDQ	Strengths and Difficulties Questionnaire
SEM	Standard Error of Means
SEV	Sociaal Emotionele Vragenlijst
SNAP-25	Synaptosomal-Associated Protein - 25
SPARCLE	Study of Participation of Children with Cerebral Palsy Living in Europe
SPASM	Support Programme for Assembly of a database for Spasticity Measurement
SV2A	Synaptic Vesicle glycoprotein 2A
TS	Tardieu Scale
UMN	Upper Motor Neuron
US	Ultrasound
VAS	Visual Analogue Scale
WHO	World Health Organization

CHAPTER I

GENERAL INTRODUCTION

CEREBRAL PALSY

Cerebral palsy (CP) is defined as a static, but often changing disorder of movement and posture due to a defect or lesion to the developing fetal or infant brain.¹ It is a major health problem as it affects 1 in 400 children making it the most common developmental disorder associated with lifelong disability.² The disorder can result from various insults to different areas within the developing central nervous system (CNS), partially explaining the variety in its clinical presentation.³ Causes of CP differ to some degree according to their time of onset (in utero, during delivery, during the first two years of life) and their clinical subtype. Although CP can be caused by a single causative factor (e.g. intracranial bleeding, perinatal stroke, congenital malformations, intrauterine infection, extreme prematurity, traumatic brain injury), it is most often caused by the interaction of genetic values and multiple environmental stressors.⁴ A specific hypoxic event associated with immediate and irreversible cell death explains the etiology of CP in less than 50%.^{5, 6}

Children usually present with slow motor development, abnormal muscle tone, muscle weakness, and disturbances in posture, although difficulties in swallowing and poor oromotor skills often precede these more noticeable abnormalities.⁷ Diagnosis is based on a complete history, thorough physical examination and additional investigations.³ Ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT), and diffusion tensor imaging (DTI) can be used to assess the extent of CNS damage as more than 80% of the children with CP have neuroimaging abnormalities, most often isolated white-matter damage.^{8, 9} The Surveillance of Cerebral Palsy in Europe (SCPE) has classified CP into three main groups: dyskinetic, ataxic, and spastic (table 1.1).¹⁰ The latter is the most common as 70–80% of the children with CP have spastic clinical features.¹¹ The SCPE states that at least two of the following clinical signs have to be present in spastic CP: abnormal pattern of posture and/or movement, increased tone, and pathological reflexes. The spastic CP syndromes can be further classified according to their topographic distribution. In bilateral spastic CP both sides of the body are involved whereas in unilateral CP only one side of the body is involved.¹⁰

Table 1.1 Classification of CP subtypes according to the SCPE¹⁰

Spastic CP is characterized by at least two of the following:

- Abnormal pattern of posture and/or movement
- Increased tone (not necessarily constant)
- Pathological reflexes (increased reflexes: hyperreflexia and/or pyramidal signs e.g. Babinski response)

Spastic CP may be either bilateral or unilateral:

- Spastic bilateral CP: Limbs on both sides of the body are involved
- Spastic unilateral CP: Limbs on one side of the body are involved

Ataxic CP is characterized by both:

- Abnormal pattern of posture and/or movement
- Loss of orderly muscular coordination so that movements are performed with abnormal force, rhythm, and accuracy

Dyskinetic CP is dominated by both:

- Abnormal pattern of posture and/or movement
- Involuntary, uncontrolled, recurring, occasionally stereotyped movements

Dyskinetic CP may be either dystonic or choreo-athetotic:

- Dystonic CP is dominated by both: Hypokinesia (reduced activity, i.e. stiff movement) and hyper-tonia (tone usually increased)
 - Choreo-athetotic CP is dominated by both: Hyperkinesia (increased activity, i.e. stormy movement) and hypotonia (tone usually decreased)
-

SPASTICITY

Definition

Before considering the definitions of spasticity the concept of the upper motor neuron (UMN) is discussed. An UMN is a neuron of any long descending tract that controls movement and muscle tone, i.e. the pyramidal and parapyramidal tracts. Damage to these tracts leads to a so called UMN syndrome, which can include both negative phenomena, like weakness, impaired fine-motor function, and difficulty in isolating individual movements and positive phenomena, like hyperreflexia, clonus, and spasticity.

The most often cited definition of spasticity is the one by Lance who defined spasticity in 1980 as a motor disorder characterized by a velocity dependent increase in the tonic stretch reflex (muscle tone) with exaggerated tendon jerks, resulting from hyper excitability of the stretch reflex, as one component of the upper motor neuron syndrome.¹²

However, in 2005 the Support Programme for Assembly of a database for Spasticity Measurement (SPASM) project came to the conclusion that the evidence generated since 1980 justified an update of the definition by Lance.¹³ Recent research suggests that spasticity is not a pure motor disorder and does

not exclusively result from hyper excitability of the stretch reflex. Furthermore, the phenomenon of velocity dependence is not exclusive to stretch reflex hyper excitability. Therefore, the SPASM project proposed the following definition: a disordered sensori-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles.

However, several more definitions of spasticity are used and debate continues on which one is most correct. An important contributing factor to the lack of an universal and more precise definition of spasticity is the fact that its pathophysiology remains not fully elucidated.

Etiology

Again, an UMN is a neuron of any long descending tract that controls movement and muscle tone, i.e. the pyramidal and parapyramidal tracts. A lesion of the pyramidal tracts (the corticospinal tracts) results in clumsiness, modest weakness, some exaggeration of deep tendon reflexes, and a Babinski sign, but does not result in spasticity. Lesions of the parapyramidal tracts however do result in spasticity. The parapyramidal tracts consist of the medial and dorsal reticulospinal, the rubrospinal, the vestibulospinal, and the tectospinal tracts. These descending pathways synapse upon interneural networks within the spinal cord that control spinal stretch, flexor, and extensor reflexes. Normally, the supraspinal inhibitory and excitatory inputs are balanced. However, in case of a lesion of these tracts a state of net disinhibition of spinal reflexes develops, which can cause spasticity.

When studying the anatomy of the parapyramidal tracts, one very rapidly realizes that there are significant differences in localizations of these fiber tracts in the different atlases.¹⁴ This is mainly due to the fact that findings in animals (cats, macaques) were extrapolated to humans. Before the introduction of advanced MRI techniques, studying white matter anatomy was limited to the dissection of formalin-fixed parts of the CNS. Large fiber tracts, like the pyramidal tracts, are therefore well studied in man, but the smaller and not neatly organized tracts, like the parapyramidal tracts, are not. However, with the introduction of DTI the direction of white matter fibers can now be shown. Using this technique Mamata et al were able to provide us with a detailed map of these structures in man.¹⁵ Studying small parapyramidal tract traumas in humans by means of DTI should provide further insight in the etiology of spasticity.

Signs and symptoms

Spasticity can cause pain, sleeping disorders, and increased energy requirements.¹⁶ Furthermore, ease of care is impeded as spasticity can interfere with positioning, transfers, dressing, and body hygiene. Additionally, spasticity can lead to contractures, subluxations, pressure sores, and heterotopic calcifica-

tions.¹⁷ There is an implicit, but yet not fully established causal relationship between spasticity and activity limitations and participation restrictions.^{13, 18}

MANAGEMENT OF SPASTICITY

Background

Management of spasticity begins with the evaluation of the necessity to treat. This is done by a multidisciplinary management team, which includes the patient and the caregivers. There are two scenarios in which spasticity should not be treated. First, when there is no interference with function, comfort, or care. Second and perhaps seemingly illogical, when “useful spasticity” is adding function in stead of restricting it. However, when spasticity, along with other positive motor phenomena of the UMN syndrome, has a significant negative impact on the functioning of a child, it represents an important therapeutic target. Regardless of the selected management option, the goal is to optimize function, ease care giving, alleviate pain, and prevent secondary problems like contractures and subluxations. It is important to set realistic, attainable goals desired by both the child and his care-givers. At each stage of goal setting, treatment planning, and plan modification, it is necessary to obtain information not only about the clinical aspects of spasticity, but also about psychosocial factors, such as participation of the child in daily life, his coping strategies, and the stress handling capacity of his family. Only then will the chance of treating every unique case successfully be highest.

Common treatment options in the management of spasticity are orally administered drugs (Baclofen, Diazepam, Dantrolene, and Tizanidine), intramuscular chemodenervation agents (alcohol, phenol, and Botulinum Toxin A), intrathecally administered drugs (Baclofen), and neurosurgery (selective dorsal rhizotomy).³

Orally administered drugs

Several orally administered drugs with various mechanisms of action are available for the management of spasticity in children with CP, i.e. Diazepam, Baclofen, Dantrolene, and Tizanidine. Diazepam, a post-synaptic GABA-a receptor agonist, is considered the most useful oral anti-spasticity agent in CP.^{19, 20} It helps against muscle stiffness, flexor and extensor spasms, pain, and insomnia. Oral Baclofen, a pre-synaptic GABA-b receptor agonist, is more suited to treat spasticity related to spinal dysfunction and is therefore less useful in children with CP.^{21, 22} The evidence on the efficacy of these drugs remains scarce and weak, and adverse drug reactions (like drowsiness, sedation, and muscle weakness) are common.^{23–25}

Injectable chemodenervation agents

Two strategies of injecting anti-spasticity agents are presently used, both causing temporary chemodenervation, i.e. the blockage of nerve-muscle transmission. Ethyl alcohol or phenol can be injected perineurally where they promote axonal degeneration.^{3, 26} Benefits can last for a few weeks up to over two years.^{27–29} The main drawbacks of this method are the necessity to identify the nerve using electrical stimulating and the significant risk of permanent post-procedure pain or paresthesia.²² Botulinum toxine A and B (BTX-A and B) are injected intramuscularly. They disable the sensitive factor attachment protein-25 (SNAP-25) and thereby prevent the release of acetylcholine from the pre-synaptic vesicle at the neuromuscular junction.³⁰ Clinical effects are usually observed after 2–5 days, last for 16–24 weeks, and are more noticeable in lower extremities than upper extremities.^{31–35} Although the functional improvements seen in randomized controlled trials are modest, this is most likely due to limitations of study design rather than by the effectiveness of the therapy itself.²² An easily administrable outcome instrument capable of measuring change on domains of interest is still lacking. Furthermore, BTX-A therapy is not without risks. A recent and large study found that 6% of the children treated with BTX-A develop systemic adverse events, mainly respiratory complications and bowel and bladder incontinence.³⁶

Intrathecaly administered drugs

In case of intrathecal Baclofen (ITB) therapy a pump is implanted subcutaneously or subfacially in the abdomen which delivers Baclofen directly to the intrathecal space via a catheter. This has the large advantage of by-passing the blood-brain-barrier (BBB). Orally administered Baclofen passes the BBB poorly and results in high blood levels (hence side-effects) and almost undetectable cerebrospinal fluid levels of Baclofen (hence low treatment effects).³⁷ In ITB, administration of a hundredth part of the dose of oral Baclofen is sufficient to relieve spasticity and therefore the side-effects seen when Baclofen is administered orally are prevented.³⁸ Children with intractable lower extremity spasticity who show significant response to a test treatment are considered candidates. Nevertheless, criteria describing the ideal candidate are still lacking.³⁹ Several large trials have shown that ITB is able to reduce spasticity.^{40–42} Furthermore, in a prospective, randomized controlled trial by the Dutch study group on spasticity functional benefits of ITB were shown.^{43–45} It was found that ITB reduces individually formulated problems, relieves pain, and improves ease of care and certain domains of health related quality of life. However, as recently stated by Miller, the follow-up on ITB treatment so far has been relatively short-term regarding that this is a treatment probably going to be continued for a 50–60 year period.⁴⁶ It is not clear whether or not benefits of therapy are still present

at the very long-term nor is the course over time. Also, the impact of accumulation of more and less severe complications, hospital visits, and hospitalizations on the enthusiasm of the caregivers for ITB treatment remains uncertain.

Furthermore, ITB carries a small but clinically significant risk of complications. Frequencies and severities of surgical complications, drug adverse events, and drug-delivery system-related complications vary significantly between studies.⁴⁷ In general, ITB is generally considered a high risk/high gain treatment.⁴⁸

Neurosurgery

Since its first description by Foerster in 1913, selective dorsal rhizotomy (SDR) has been modified by various surgeons and has become a standard neurosurgical procedure to treat spasticity in children with CP.^{49, 50} SDR is mainly performed at the lumbar level to reduce spasticity in patients with bilateral spasticity. A multilevel laminotomy/laminectomy exposes the dorsal roots (L2-S2) which are then separated into different rootlets. Those eliciting excessive EMG activity are incompletely transected, hereby reducing the excitatory input to the spinal cord. SDR reduces spasticity and improves gait pattern, range of motion, and gross motor function.⁵¹ It must be noted that considerable cooperation of the patient is required to successfully complete the postoperative rehabilitation program. A recent review found a significant amount of spinal abnormalities and back-pain in children who have undergone SDR.⁵² However, the relationship between the two remains unclear.

In chronic pain medicine, a radiofrequency lesion of the dorsal root ganglion (RF-DRG) is considered an alternative to SDR. RF-DRG has been used to treat chronic pain for over 30 years.⁵³ The RF-DRG is a simple and safe treatment option with little side-effects.⁵⁴ In the 1980's several authors reported that the same procedure might be able to treat spasticity in adult patients.^{55, 56} More recently, RF-DRG showed to alleviate hip flexor spasms in 2 children with CP.⁵⁷ Further research with regard to the role of RF-DRG in the treatment of spasticity is required.

EVALUATION OF SPASTICITY MANAGEMENT

If you cannot measure it, you cannot control it. (John Grebe, 1990)

Evaluating interventions in children with CP, poses somewhat of a challenge as many health-care disciplines are involved and effects can appear at physiological, functional, social, and / or behavioral levels. With regard to spasticity, we are not absolutely sure what we are dealing with, let alone how we should measure it. This is probably best illustrated by the plethora of scales developed

to assess spasticity. A recent review found 37 clinical scales claiming to assess spasticity or spasticity associated functions.⁵⁸ However, these scales have not been evaluated to a sufficient extent and for many scales reliability data is missing, especially concerning test-retest reliability. One can understand this to be a huge problem when using these scales as an outcome measure for spasticity management in children with CP.

In accordance with the currently often used WHO international classification of functioning, disability and health (ICF), the scales are classified into those assessing tone (ICF body functions and structure) and those assessing functioning (ICF activity and participation). Recently, a modified ICF model has been proposed which also incorporates quality of life (fig 1.1).⁵⁹ Quality of life of children with CP will be discussed later on.

Figure 1.1 The WHO ICF including human development and QoL

Assessment of tone

The most often used scales concentrate on assessing tone, i.e. the Ashworth Scale, the Modified Ashworth Scale (MAS) and the Tardieu Scale (TS). The Ashworth Scale is a 5-point rating scale (0–4), which measures resistance to passive movement. Although the most commonly used, the methodological quality of the Ashworth Scale is doubtful. It does not measure spasticity exclusively, it has low interrater reliability, and it lacks precision and sensitivity for measuring smaller changes in spasticity.^{60–62} A recent study showed both the Ashworth Scale and the MAS to not be very reliable and therefore assessment of spasticity using these ordinal rating scales should be interpreted with great caution.⁶³ The TS is

a 6-point rating scale which describes the muscle reaction to passive stretch at different speeds. Recently, it has been shown to be more effective than the Ashworth scale in identifying the presence of spasticity, but again is not capable of measuring the severity of spasticity.⁶⁴ Furthermore, it is a very time-consuming method and therefore its feasibility is questioned, especially when applied to children.⁶²

Assessment of functioning

Several other scales focus on functioning after spasticity treatment. The ones most often used in children with CP are the Gross Motor Function Measurement (GMFM) and the Pediatric Evaluation of Disability Inventory (PEDI). The GMFM is widely accepted as the best available quantitative method. However, in infants with CP it was shown that spasticity is only marginally related to gross motor function development.⁶⁵ Especially in severely affected children the GMFM is of limited value.⁶⁶ The PEDI is a generic questionnaire which measures the functioning, health, and self care in chronically ill children with disabilities. It is administered through a structured interview with a parent. A recent review found the PEDI to be valid, reliable and responsive to change.⁶⁷ The main drawback of the PEDI is that it takes over 45 minutes to complete, making it not very suitable in a busy outpatient clinic.

Assessment of side-effects

Besides evaluating the effect of treatment, the physician has to be aware of possible side-effects. These are not uncommon after routine treatments of spasticity as mentioned before.

MORE THAN MOTOR PROBLEMS ALONE

In addition to their motor problems, children with CP often have a spectrum of accompanying problems for which a multidisciplinary approach is needed. Epilepsy in children with CP is common (up to one third), has an early onset, and requires prolonged and intense pharmaceutical treatment.⁶⁸ Recent studies have established the relationships between CP and impaired non-verbal intelligence, learning disabilities, impaired memory and language functioning, and disturbed executive functions.⁶⁹ Feeding problems are widespread in children with CP; more than 1 out of 10 depends on gastrostomy tube feeding and around 40 percent has an abnormal body mass index (BMI).⁷⁰ Orthopaedic problems are highly prevalent amongst children with CP. The most common deformity is the equinus, but hip deformities and spastic scoliosis are far from rare either.⁷¹ It is now recognized that 4 out of 10 children with CP have at least

one clinically significant sleeping disorder.⁷² A recent Dutch study investigated sexuality in young adults with CP and found 80% to report physical problems with sex and 45% to report emotional inhibition to initiate sexual contact.⁷³ There is increasing interest in the consequences of the combination of these accompanying problems and the previously discussed motor problems on the quality of life (QoL) of children with CP.

QUALITY OF LIFE

The WHO defines QoL as “an individual’s perception of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns”.⁷⁴ Technically speaking QoL is not a definition; it is a concept, an invention of the human mind to construct a model of the world. As with all human inventions, it is not perfect and therefore QoL does not represent one single truth. Nevertheless, attempts should be made to capture and analyse this QoL in the best way possible as it may expose problem areas in chronically ill children and lead to treatment opportunities.

There are several instruments available to assess QoL of children with CP. Two well established and often used instruments are the Child Health Questionnaire (CHQ) and the KIDSCREEN. The CHQ is a generic QoL instrument which measures 14 unique physical and psychosocial concepts.⁷⁵ All concepts are scored on a 0–100 scale with higher scores reflecting better QoL. Physical and psychosocial summary scores can be derived from the separate CHQ profile scores which have a mean of 50 and a standard deviation of 10 in the general population. The KIDSCREEN is a modern, generic QoL instrument, which uses questions based on focus-groups with children and adolescents held all over Europe.^{76–78} It focuses entirely on subjective perceptions, has shown to possess excellent psychometric properties, can be used for both disabled and non-disabled children, and can be reported by both the children themselves and their caregivers.^{76–79}

Previous studies have assessed QoL of children with CP. Several smaller studies found contradicting results.^{80–83} The largest study so far (SPARCLE study, 7 European countries, KIDSCREEN-52) found that QoL of children with CP aged 8–12 years is, on average, similar to that of children in the general population on practically all domains.⁸⁴ This study provided clues that children with CP might have a slightly better school environment, but experience lower autonomy. Specific factors were found to be associated with lower QoL in certain domains, e.g. pain is associated with less QoL in the physical and psychological well-being and self-perception domains.⁸⁵ Greater limitations, on the other hand, lead to higher or lower QoL depending on the domain. However, impairment and pain can only explain a small amount of variance in QoL, which is therefore likely to be largely determined by social and environmental factors.

CHAPTER I

Unfortunately social and environmental factors can differ significantly between countries and even regions and KIDSCREEN QoL results for Dutch children with CP are still lacking.

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CHAPTER I

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CHAPTER II

AIM AND OUTLINE OF THE THESIS

AIM AND OUTLINE OF THE THESIS

In the general introduction a brief overview of clinical and therapeutic aspects of CP has been provided. Furthermore, gaps, concerns, and controversies in current knowledge were highlighted. The aim of this thesis was to address and study some of these issues in the population of approximately 100 children with CP who are seen at the outpatient clinic of the Maastricht University Medical Centre (MUMC).

As a first step of this thesis the basic characteristics of these children were collected, which was followed by a study to see how these children cope with their often severe disabilities and limitations. Therefore, in *chapter III* the psychosocial adjustment of the Dutch sample of children with CP is described.

Chapter IV and V concentrate on the management of spasticity in CP. In *chapter IV* the effects of a percutaneous radiofrequency lesion adjacent to the dorsal root ganglion on spasticity and pain is investigated as it was hypothesized that this could serve as an alternative to the conventional SDR. The results of a pilot study in 17 children with CP are described. In *chapter V* two cases of dyskinetic CP are reported on in which an anti-convulsant drug (Levetiracetam) led to an impressive improvement of balance control and fine motor skills.

Chapter VI to VIII focus on the evaluation of spasticity management. In *chapter VI* the usefulness of a simple visual analogue scale to evaluate the effects of BTX-A treatment on spasticity is demonstrated. In *chapter VII* three cases of a never before reported side-effect of BTX-A treatment are described. *Chapter VIII* reports on the long-term follow-up on the beneficial effects of ITB treatment in children with intractable spastic CP.

In *chapter IX* the QoL of children with CP living in the Southern part of the Netherlands is described, as the Netherlands did not participate in the SPARCLE study.

CHAPTER III

PSYCHOSOCIAL ADJUSTMENT IN A DUTCH SAMPLE OF CHILDREN WITH CEREBRAL PALSY

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ABSTRACT

Background

Over the last couple of years, there has been increasing interest for QoL of children with CP. Psychosocial adjustment in these children remains underrepresented in current literature.

Aims

To describe psychosocial adjustment in children with CP by means of the Psychosocial Adjustment and Role Skills Scale - III (PARS-III), to describe the psychometric properties of this questionnaire, to identify a cut-off score for psychosocial maladjustment, and to investigate the relationship between patient characteristics (i.e. predictive factors) and psychosocial adjustment.

Methods

The parents of 93 children with CP (59 boys, 34 girls; mean age 12.3 years, SD 3.8, 4–18; GMFCS 1: 28, 2: 5, 3: 19, 4: 18, 5: 23) completed the PARS-III and the Child Behavior Checklist (CBCL) concerning the psychosocial and behavioral functioning of their child.

Results

Cronbachs alpha-coefficient for the PARS-III was 0.89 indicating good internal consistency. High correlation with the CBCL was found. Confirmatory factor analysis confirmed the 6 domain structure of the PARS-III. Overall, children with CP achieved lower psychosocial adjustment scores compared to healthy children. A cut-off score (1 SD below the mean) of 78 was found. When predicting psychosocial maladjustment in children with CP, less gross motor function, hand function, communication skills, and bilateral involvement of CP are the most important factors, but these can only explain 36% of variation in psychosocial adjustment.

Conclusion

Using the by-proxy version of the PARS-III it was found that children with CP are reported to achieve lower psychosocial adjustment scores than healthy children.

INTRODUCTION

Over the last couple of years, there has been increasing interest for health outcomes in children with cerebral palsy (CP).¹ More and more, treatments are evaluated in terms of health, Quality of Life (QoL) and health related QoL. The World Health Organization (WHO) defines QoL as “an individual’s perception of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns”.² Extensive research concerning QoL of children with CP has been done. The largest study so far (SPARCLE study, 7 European countries, KIDSCREEN-52) found that QoL of children with CP aged 8–12 years is, on average, similar to that of children in the general population on practically all domains.³

Another important concept is psychosocial adjustment, defined as the adaptive task of coping with upsetting feelings and frustrations aroused by the illness.⁴ Contrary to QoL, psychosocial adjustment remains underrepresented in current literature. Although strongly related, psychosocial adjustment and QoL are distinct entities, which will hopefully be illustrated by the following example. Children with CP frequently have hip deformities which may cause pain.⁵ The way of coping with this pain is different for every child. Some children with little hip deformity will become very anxious when they have to put weight on their hip joint and will therefore not participate in playing outdoors, while others with severe hip deformity will ignore the pain, play outside and establish new friendships (the so called “disability paradox”).⁶ Hence, psychosocial adjustment determines whether and to what extent pain influences QoL. It is the result of a complex process in which children attempt to meet the demands of their illness with their emotional/social resources and coping strategies. In other words, better coping strategies will lead to higher QoL. Thus, in order to understand a child’s QoL and to eventually be able to improve it, one must understand why and when children will apply appropriate psychosocial adjustment.

The main problem in this research area is that there are few standardized instruments specifically developed for these children with a chronic illness. Using the Child Behavior Checklist (CBCL) Sigurdardottir et al found a prevalence of 40 to 50% of substantial behavioural or emotional difficulties in preschool children with CP.⁷ However, the primary aim of the CBCL is to identify and diagnose psychopathological behaviour.⁸ It does not take into account the stress and emotional reactions part of normal adjustment to a chronic illness.^{9, 10} As such, the CBCL is prone to over identify pathological behaviour. Using the Strengths and Difficulties Questionnaire (SDQ) Parkes et al found that over a quarter of children with CP aged 8–12 years experience significant psychological problems, mainly peer problems, hyperactivity, and emotional problems.¹¹ The major drawback of the SDQ is that it measures general behaviour problems without special consideration of illness-related factors.¹² As the CBCL, it may over identify pathological behaviour.

A questionnaire specifically developed to measure psychosocial adjustment in children with a chronic illness is the Psychosocial Adjustment and Role Skills Scale - III (PARS-III).¹³ Its main strength is that it includes domains important to the psychosocial adjustment of children with a chronic illness and leaves out items based on physical symptoms like pain, fatigue, and headaches.¹⁴

Recently, Hendriksen et al found the PARS-III to be a reliable and valid index of psychosocial adjustment in boys with Duchenne Muscular Dystrophy (DMD), a fatal, X-linked, muscle disorder, which affects approximately 1 in 3,500 children, almost all boys.¹⁵ On the basis of this result the current study was conducted with the following aims. The first aim is to describe psychosocial adjustment in a Dutch sample of children with CP using the PARS-III questionnaire and to describe its psychometric properties. Secondly, in order to provide a first step towards identifying psychosocial adjustment profiles in different patient populations, a brief comparison to boys with DMD will be made. Thirdly, a clinical useful cut-off score for psychosocial maladjustment in children with CP will be identified. Finally, the relationship between patient characteristics (i.e. predictive factors) and psychosocial adjustment will be investigated.

METHODS

Design

This cross-sectional study was approved by the Medical Ethics Committee (MEC) of the Maastricht University Medical Centre (MUMC) according to Dutch governmental guidelines.

The parents of all 94 children with CP (aged 4–18 years) seen at the outpatient clinic of the MUMC were informed about the study and asked to participate. All except one agreed and were sent the PARS-III and the CBCL questionnaires.

Data concerning the psychosocial adjustment of 63 Dutch boys with DMD and 95 healthy children were collected at an earlier stage.¹⁵

Measures

Psychosocial Adjustment and Role Skills Scale - III

The PARS-III was specifically developed to measure psychosocial adjustment in children (aged 5 to 18 years) with a variety of chronic physical illnesses.^{13, 14} It is a brief - 28-item - parent-completed questionnaire of which all items use a four-point ordinal rating scale: “never or rarely”, “sometimes”, “often”, or “always or almost always”. The total score is the summation of the scores assigned (from 1 to 4) to each item with higher scores indicating more adjusted functioning.

Summation of specific items also yields six factor-derived psychosocial subscales: peer relations, dependency, hostility, productivity, anxiety/depression, and withdrawal. Reliability and validity are described as adequate to good, e.g. alpha coefficient for the total score is 0.88 ($n=449$).^{13, 14}

Child Behaviour Checklist

The Achenbach CBCL is one of the most widely used measures for the assessment of behavioral problems and domains of competence.⁸ Based on a 113-item questionnaire, a total problem scale, two broadband scales (internalising and externalising behaviour problems) and eight narrowband scales (anxiety/depression, withdrawal, physical complaints, social problems, thought problems, attention problems, rule breaking behaviour, aggressive behaviour) can be derived. For the purpose of this study only the narrowband scales were used. Resulting standardised T-scores are defined as “borderline” (67 to 70) and “clinical” (larger than 70, that is, above the 98th percentile).

Participants

Children with CP

The major patient characteristics were collected from the medical files of the children and are displayed in Table 3.1. The 93 children with CP consisted of 59 boys and 34 girls with a mean age of 12.3 years (SD 3.8; 4–18). Forty-four per cent of the children with CP were wheelchair dependent and 52% had a cognitive level below 70. The percentages of children scoring in the clinical range on the eight narrowband scales of the CBCL (above the 98th percentile) are displayed in Table 3.2. It can be seen that for the areas of physical complaints (14%), social problems (8%) and attention problems (5%) larger proportions of children with CP scored above the 98th percentile than would be expected.

Boys with DMD and healthy children

The parents of 63 boys with DMD were recruited from the Dutch Parent Project Muscular Dystrophy, which is a parent advocacy group. The mean age of the 63 boys with DMD was 10.8 years (SD 4.1; 3–23); 65% were wheelchair dependent. The parents of 100 healthy children were recruited at random from three different schools in the Southern part of the Netherlands; 95 agreed to participate. The mean age of the 48 healthy boys and 47 healthy girls was 7.7 years (SD 2.8; 4–13).

Table 3.1 Characteristics of the children with CP

	Mean (range) Frequency (%)		Mean (range) Frequency (%)
Numer of patients	93	Age (years)	12.3 (4–18)
Sex		Sensory disability	
Male	59 (63%)	Visual	15 (16%)
Female	34 (37%)	Auditory	2 (2%)
Type CP		Feeding	
Spastic unilateral	31 (33%)	I Without difficulties	75 (81%)
Spastic bilateral	59 (63%)	II Significant Difficulties	19 (21%)
Dyskinetic	2 (2%)	III Stoma	6 (7%)
Ataxic	1 (1%)	Missing	1 (1%)
Cognitive level		Pain / discomfort	
< 50	23 (25%)	None	58 (62%)
50–70	25 (27%)	Some - severe	33 (36%)
>70	45 (48%)	Missing	2 (2%)
GMFCS		Communication Skills	
1	28 (30%)	I Normal	57 (62%)
2	5 (5%)	II Problems	19 (20%)
3	19 (20 %)	III Alternatives	7 (8%)
4	18 (19%)	IV None	9 (10%)
5	23 (25%)	Missing	1 (1%)
Wheelchair dependent		Level of hand functioning	
Yes	41 (44%)	I No limitations	18 (19%)
No	52 (56%)	II Limitations with fine motor task in both hands	26 (28%)
Family composition		III Needs assistance in performing tasks	20 (22%)
Two parents family	85 (91%)	IV Needs assistance and makes use of adaptive equipment	6 (7%)
One parent family	4 (4%)	V Requires assistance in everything	21 (23%)
Missing	4 (4%)	Missing	2 (2%)
Epilepsy		Living area	
None the last year	72 (77%)	Urban	47 (52%)
< 1 / month last year	14 (15%)	Countryside	44 (47%)
> 1 / month last year	7 (8%)	Missing	2 (2%)
School type		Occupation parents	
Normal education	33 (36%)	>1 parent works fulltime	59 (63%)
Special education	57 (61%)	Other situation	31 (33%)
Missing	3 (3%)	Missing	3 (3%)

Table 3.2 Percentages of children with CP (N= 86) scoring in the clinical range of the CBCL narrow-band scales (above the 98th percentile)

Scale	%	Scale	%
Anxiety / depression	1%	Thought problems	1%
Withdrawal	3%	Attention problems	5%
Physical complaints	14%	Rule breaking behavior	0%
Social problems	8%	Aggressive behavior	2%

Statistical analysis

All data were entered into SPSS 18.0 for statistical analysis (RH). The accuracy of data entry was randomly checked and found correct by a different researcher (JH). Cronbach's alpha was used to calculate the internal consistency of the PARS-III. Confirmatory factor analysis (CFA, AMOS 17) was performed to confirm the six domains of psychosocial functioning on the PARS-III questionnaire. Factor loadings above 0.6 were considered high and factor loadings below 0.4 were considered low. As an indication for criterion validity of the PARS-III bivariate correlations with the eight narrowband scales of the CBCL were calculated.

Subsequently, independent sample T tests were used to assess differences between PARS-III scores of children with CP, boys with DMD and healthy children. P-values below 0.05 were considered significant.

In order to establish a cut-off score, the same method as Witt et al, Pless et al and Hendriksen et al was used, meaning that 1 SD below the group mean is used as a cut-off score for poor psychosocial adjustment.¹⁵⁻¹⁷

Finally, univariate and multivariate (forward entry, dummy variables) model testing was used to identify patient characteristics (Table 3.1) predictive for poor psychosocial adjustment in children with CP.

RESULTS

Psychometric properties of the PARS-III when used for children with CP

Good internal consistency for the total PARS-III score was found: a Cronbach's alpha of 0.89. For the six subscales the alpha coefficient was 0.81 for peer relations; 0.56 for dependency; 0.83 for hostility; 0.80 for productivity; 0.76 for anxiety/depression and 0.76 for withdrawal.

CFA confirmed the six domains of psychosocial functioning on the PARS-III questionnaire (Figure 3.1). Except for questions 6, 13 and 20, all factor loadings were adequate (8) and high (18). Exploratory factor analysis showed that question 6 did load on the domain withdrawal. Questions 13 and 20 did not load on any.

Figure 3.1 Confirmatory factor analysis of the structure of the PARS-III questionnaire
P1-P28: questions on the PARS-III questionnaire; PR = peer relations; Dep = dependency; Host = hostility; Prod = productivity; With = withdrawal; Anx = anxiety and depression. Numbers indicate factor loadings.

As an indication for criterion validity of the PARS-III bivariate correlations with the eight narrowband scales of the CBCL were calculated (Table 3.3). It can be seen that all correlations are in the expected directions (low adjustment scores on the PARS-III correlate with high problem scores on the CBCL). The PARS-III total score correlates significantly ($r = -0.29$ to $r = -0.59$) with all narrowband scales of the CBCL. Furthermore, it can be seen that the CBCL scale for social problems correlates highest with the PARS-III domain peer relations ($r = -0.50$). Also, as can be expected, the CBCL scale for aggression correlates highest with the PARS-III domain hostility ($r = -0.68$), the CBCL scale for anxiety/depression with the PARS-III domain anxiety ($r = -0.58$), and the CBCL scale for withdrawal with the PARS-III domain withdrawal ($r = -0.43$).

Table 3.3 Bivariate correlations (r) between the PARS-III and the CBCL in children with CP

		P A R S - I I I						
		Peer	Dep	Host	Prod	Anx/Depr	Withd	Total
C B C L	Anx/Depr	-0.23 *	-0.29 **	-0.12	-0.03	-0.58 ***	-0.35 ***	-0.39 ***
	Withd	-0.39 ***	-0.45 ***	-0.16	-0.24 *	-0.40 ***	-0.43 ***	-0.52 ***
	Somatic	-0.40 ***	-0.04	-0.16	-0.37 ***	-0.21	-0.27 *	-0.37 ***
	Social	-0.50 ***	-0.38 ***	-0.42 ***	-0.24 *	-0.49 ***	-0.37 ***	-0.59 ***
	Thought	-0.03	-0.32 ***	-0.21	-0.13	-0.15	-0.35 ***	-0.29 *
	Attention	-0.22	-0.54 ***	-0.46 ***	-0.32 ***	-0.27 *	-0.34 ***	-0.52 ***
	Rule	-0.13	-0.57 ***	-0.39 ***	-0.07	-0.34 ***	-0.28 **	-0.43 ***
	Aggress	-0.07	-0.52 ***	-0.68 ***	-0.24 *	-0.40 ***	-0.29 **	-0.56 ***

All correlations are in the expected directions (low adjustment scores on the PARS-III correlate with high problem scores on the CBCL). * = $p < .05$; ** = $p < .01$; *** = $p < .001$; Peer = Peer Relations; Dep = Dependency; Host = Hostility; Prod = Productivity; Anx/Depr = Anxiety/Depression; Withd = Withdrawal; Somatic = Somatic Complaints; Social = Social Problems; Thought = Thought Problems; Attention = Attention Problems; Rule = Rule-breaking Behavior; Aggress = Aggressive Behavior

Psychosocial adjustment profiles of children with CP, boys with DMD, and healthy children

Children with CP achieve significantly lower psychosocial adjustment scores when compared to healthy children ($p < 0.001$), especially in the domains peer relations ($p < 0.001$), anxiety/depression ($p < 0.01$), withdrawal ($p < 0.001$), and productivity ($p = 0.02$) (Table 3.4). In general, boys with DMD do not differ significantly from children with CP ($p = 0.93$). However, when looking at the domains of psychosocial adjustment, children with CP score significantly lower than boys with DMD on peer relations ($p = 0.03$).

Table 3.4 Comparison of psychosocial adjustment scores in healthy children, children with CP and boys with DMD

	Healthy Children			Children with CP				Boys with DMD				
	N	Mean	SD	N	Mean	SD	Sign1	N	Mean	SD	Sign1	Sign2
Peer relations	93	11.9	2.4	87	8.6	2.9	***	62	9.6	2,8	***	*
Dependency	93	13.5	2.0	85	12.9	2.1	ns	60	12.4	2,1	**	ns
Hostility	93	21.4	2.9	85	21.3	3.0	ns	63	20.6	3,4	ns	ns
Productivity	91	11.0	2.3	87	10.0	2.9	*	60	10.7	2,5	ns	ns
Anxiety	93	22.5	1.7	87	21.6	2.4	**	63	21.9	1,9	ns	ns
Withdrawal	91	15.6	1.0	91	14.2	2.0	***	60	14.4	1,9	***	ns
Total	88	95.7	7.1	77	88.6	10.4	***	55	88.5	9,9	***	ns

N = number of cases, * p < 0.05, ** p < 0.01, *** p < 0.001, ns = not significant

Sign1 = significance compared to healthy children

Sign2 = significance compared to children with CP

Establishing a cut-off score

Both Witt et al, Pless et al, and Hendriksen et al calculated 1 SD below the group mean and used this number as a cut-off score for psychosocial maladjustment.¹⁵⁻¹⁷ They found cut-off scores of respectively 73.1 and 72.3. In this current study this method would result in a cut-off score of 78 (88.6 – 10.4) identifying the 16 % (1 SD) of the children with CP showing the worst psychosocial maladjustment.

Factors predictive for less psychosocial adjustment in children with CP

Using univariate and multivariate (forward entry, dummy variables) model testing it was found that the patient characteristics most predictive for lower PARS-III sub and total scores were gross motor function, level of hand function (LoH), communication skills (CS) and bilateral involvement of CP (Table 3.5). Put together in a model, these four patient characteristics could explain a significant proportion (36%) of the variation in PARS-III total scores.

Table 3.5 Patient characteristics explaining differences in PARS-III domain scores (multivariate regression analysis)

	Patient characteristic	B	SE	p	R ²	F-ratio
Peer relations	Bilateral	-2.54	0.70	0.00	0.23	12.24
	GMFCS5	-1.33	0.59	0.03		
Dependency	LoH-IV	-3.17	0.90	0.00	0.14	12.31
Hostility	CS-III	-4.20	0.96	0.00	0.38	12.36
	LoH-IV	-3.29	1.01	0.00		
	Age	0.22	0.07	0.00		
	GMFCS5	-1.59	0.64	0.02		
Productivity	GMFCS5	-1.62	0.76	0.04	0.28	10.20
	Bilateral	-1.38	0.58	0.02		
	CS-IV	-2.88	1.29	0.03		
Anxiety / depression	-	-	-	-	-	-
Withdrawal	CL<50	-1.43	0.48	0.00	0.10	8.99
Total	GMFCS5	-7.32	2.63	0.00	0.36	9.72
	Sign. feeding difficulties	-9.47	3.30	0.00		
	Bilateral					
	LoH-IV	-5.63	2.16	0.00		
		-8.81	4.08	0.00		

Bilateral = Bilateral spastic CP, LoH-IV = Level of Hand function level IV: needs assistance and makes use of adaptive equipment, CS-III = Communication Skills level III: having to use alternative methods to communicate, CS-IV = Communication Skills level IV: no ways of communication, CL = Cognitive level, GMFCS = Gross Motor Function Classification System, B = beta, SE = Standard Error

DISCUSSION

Psychosocial adjustment of children with CP

To the best of our knowledge this is the first study describing psychosocial adjustment in children with CP using the PARS-III questionnaire for parents. It shows that children with CP are reported to achieve less psychosocial adjustment when compared to healthy children (Table 3.4). The first domain of significantly lower psychosocial adjustment is peer relations, with lower gross motor function being an important predictive factor (Table 3.5). This can be explained by the fact that participation in daily life and leisure activities, key to developing peer relations, is less in children with more physical restriction.^{18, 19}

The second domain of lower scores in children with CP was anxiety/depression. Sigurdardottir et al found lower IQ to be a risk factor for more anxiety.⁷ In the current study cognitive level was not found to be related to anxiety ($R^2 = 0.012$). In fact, none of the patient characteristics were. Possible expla-

nations might be that Sigurdardottir et al studied preschool children and used the CBCL questionnaire, which is not specifically developed to assess psychosocial adjustment.

The third domain, in which children with CP show significantly lower psychosocial adjustment scores, was withdrawal. Low cognitive level (IQ below 50) turned out to be the only predictor ($B = -1.42$; $R^2 = 0.10$), which this time is in agreement with the study by Sigurdardottir et al.⁷

Comparison to boys with DMD

Overall, children with CP do not differ significantly from boys with DMD on the PARS-III total score ($p = 0.92$). However, children with CP score significantly lower than boys with DMD on the domain peer relations ($p = 0.03$). This could be due to the fact that during the initial phases of their disease boys with DMD are able to participate almost normally in life and therefore establish more and better peer relations. Furthermore, children with CP showed a trend towards lower scores on the domain of dependency ($p = 0.09$), reflecting higher independence in boys with DMD as they are more able to live independent lives.

The cut-off score

A cut-off score (1 SD below the mean) of 78 was identified in this study. This means that children with CP scoring below 78 are at risk for psychosocial maladjustment and merit further assessment. Even though the identified cut-off score can be helpful in clinical practice, the development of clinical norms based on a demographically representative sample would be highly useful.

Predictive factors of psychosocial adjustment in children with CP

The most important predictive factor for lower psychosocial adjustment was a higher restriction in gross motor function, i.e. higher GMFCS level, bilateral involvement and worse hand function. This is a common observation in the literature.^{3, 20} A regression analysis model could explain 36% of variation in PARS-III adjustment scores, highlighting the complexity of both CP and psychosocial adjustment.

Although pain is common in children with CP (35% of studied population had moderate to severe pain complaints), it was found that pain was not a significant predictive factor for psychosocial adjustment on any of the 6 domains of the PARS-III. This is in contrast with previous studies in which pain resulted in lower QoL and more behavioral problems (measured by means of the KID-SCREEN and SDQ respectively).^{3, 11} This discrepancy between our findings and literature may be due to the fact that dichotomous pain data was used, but also due to the fact that psychosocial adjustment and QoL are different concepts. For

example, in a study by Engel et al it was shown that in adults with CP it is not the pain itself that influences psychological functioning, but the coping strategies in reaction to the pain.²¹

As already stated above, differences in psychosocial adjustment could only partially be explained using patient characteristics previously reported in literature. It is suggested that future studies should also include basic neurological substrates when investigating psychosocial adjustment. For example, for both CP and DMD it is known that the cerebellum can be involved in the pathogenesis. It has recently been shown that cerebellar injury in premature infants is associated with a high prevalence of cognitive, learning and behavioral disabilities.²² Sophisticated MRI analyses (e.g. Diffusion Tensor Imaging and connectivity analyses) would aid investigating such a relationship between the cerebellum and psychosocial functioning in children with CP. Future research should compare PARS-III scores in children with CP with and without cerebellar involvement.

Limitations of this study

This study has several limitations, some of which are almost inevitable in this field of research.

The first limitation is that the data are cross-sectional and therefore no conclusions about causal relationships can be made. Consequently, the developmental profile of psychosocial adjustment in children with CP remains unclear. A longitudinal – follow-up – study using the PARS-III questionnaire is advised in order to elucidate this developmental profile and find out whether different age periods (moving to another town, older brother going to college, hitting puberty, etc) are characterized by different psychosocial adjustment problems.

The second limitation is the sole reliance on proxy reports. The literature on the best source to evaluate QoL and psychosocial adjustment is inconsistent at best. The WHO and the International Association for Child Psychology and Psychiatry recommend that children should report their own QoL.²³ However Le Coq et al found that in 8 to 11 year old pediatric asthma patients parents were more responsive and reliable reporters on a QoL measure.²⁴ Then there is the limitation that some children might not be capable to self-report because of their age, cognitive impairments or disabilities.²⁵ In this case, proxy-reports are the only way to evaluate QoL with their parents / caregivers being the most logical source of information as they are assumed to have intimate knowledge of the child. It is now becoming more and more accepted that there is no one single truth concerning concepts like QoL and psychosocial adjustment and therefore self-reports and proxy reports are complementary.²⁶ With regard to the current study, self-reports would have been extremely difficult to obtain and interpret given the severity of disability of the majority of the children with CP.

CHAPTER III

Finally, in the absence of a golden standard for psychosocial maladjustment ROC curves cannot be produced and therefore identifying a cut-off score is arbitrary. In accordance with Witt et al, Pless et al and Hendriksen et al this study used 1 SD below the mean as a cut-off score.¹⁵⁻¹⁷ This inevitably means that 16% of the children with CP will receive further assessment. Experience will tell whether this method over-, under- or appropriately identifies psychosocial maladjustment.

CONCLUSION

This study showed the PARS-III to possess good internal consistency and criterion validity when applied to children with CP and can therefore be used for both clinical screening and research purposes. Using this by-proxy questionnaire, it was found that children with CP achieve lower psychosocial adjustment scores when compared to healthy children, especially in the subdomains peer relations, anxiety/depression, withdrawal, and productivity. Future studies should aim at unraveling the developmental profile and risk factors for psychosocial maladjustment.

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CHAPTER IV
PERCUTANEOUS RADIOFREQUENCY LESIONS
ADJACENT TO THE DORSAL ROOT GANGLION
ALLEVIATE SPASTICITY AND PAIN IN
CHILDREN WITH CP

pilot study in 17 patients

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ABSTRACT

Background

Cerebral palsy (CP) may cause severe spasticity, requiring neurosurgical procedures. The most common neurosurgical procedures are continuous infusion of intrathecal baclofen and selective dorsal rhizotomy. Both are invasive and complex procedures. We hypothesized that a percutaneous radiofrequency lesion of the dorsal root ganglion (RF-DRG) could be a simple and safe alternative treatment. We undertook a pilot study to test this hypothesis.

Methods

We performed an RF-DRG procedure in 17 consecutive patients with CP with severe hip flexor / adductor spasms accompanied by pain or care-giving difficulties. Six children were systematically evaluated at baseline, and 1 month and 6 months after treatment by means of the Modified Ashworth Scale (MAS), Gross Motor Function Measure (GMFM), and a self-made caregiver's questionnaire. Eleven subsequent children were evaluated using a Visual Analogue Scale (VAS) for spasticity, pain, and ease of care.

Results

A total of 19 RF-DRG treatments were performed in 17 patients. We found a small improvement in muscle tone measured by MAS, but no effect on the GMFM scale. Despite this, the caregivers of these six treated children unanimously stated that the quality of life of their children had indeed improved after the RF-DRG. In the subsequent 11 children we found improvements in all VAS scores, in a range comparable to the conventional treatment options.

Conclusion

RF-DRG is a promising new treatment option for severe spasticity in patients with CP. Its definitive effectiveness remains to be defined in a randomized controlled trial.

BACKGROUND

Cerebral palsy (CP) is a central nervous system deficit resulting from a non-progressive lesion in the developing brain. Although these brain lesions are static, the movement disorders that arise are not unchanging and are characterised by atypical muscle tone, posture, and movement.¹ The spastic motor type is the most common form of CP and its conventional therapeutic management may include splinting / casting, physiotherapy, occupational therapy, oral spasmolytics and anti-dystonic drugs, Botulinum Toxin-A (BTX-A) injections, orthopaedic procedures, and neurosurgical procedures. The most common neurosurgical procedures are continuous infusion of intrathecal Baclofen (ITB) and selective dorsal rhizotomy (SDR). Since its first description by Foerster in 1913, SDR has been modified by various researchers and has become a standard neurosurgical procedure to treat spasticity in patients with CP.²⁻⁵ However, as multi-level laminectomies at the L1-S1 level are often required, the procedure is invasive and can lead to complications as transient urinary incontinence, chronic low back pain, and spinal deformity.⁶⁻⁹ Furthermore, considerable cooperation of the patient is required to successfully complete the postoperative rehabilitation program.

An alternative for the SDR is a radiofrequency lesion of the dorsal root ganglion (RF-DRG), which has been used to treat chronic pain for over 30 years.¹⁰ The RF-DRG is a simple and safe treatment with little side-effects.^{11, 12} In the 1980's several authors reported that the same procedure might be used to treat adult patients with spasticity.^{13, 14} More recently, we were able to show that an RF-DRG alleviates hip flexor spasms in 2 patients with CP.¹⁵ Patients with CP can also suffer from severe pain through spasticity, bone deformities or joint subluxation, especially hip displacement and dislocation^{16, 17}, which may lead, through an enhanced processing of afferent information within the spinal cord, to secondary pain.¹⁸

We thus hypothesized that an RF-DRG may alleviate spasticity and pain in patients with CP, and we tested this hypothesis in a pilot study of 17 patients.

METHODS

Children with spastic CP were seen by a multi-disciplinary spasticity management team (child neurologist, orthopaedic surgeon, and physician assistant child neurology) of the Maastricht University Medical Centre (MUMC). Individual treatment goals were determined after a careful assessment of the aetiology, functional ability, and associated impairments as a result of the spasticity. The RF-DRG treatment was considered in children with severe hip flexor / adductor spasms accompanied by pain or care giving difficulties. The procedure was ap-

proved by the Institutional Review Board of the MUMC, according to Dutch governmental regulations and informed consent from the caregivers was obtained for each patient.

A total of 17 children were treated with RF-DRG (tables 4.1, 4.2). The severity of CP was based on the Gross Motor Function Classification System (GMFCS) for CP.^{19, 20} Hip(sub)luxation was classified according to the morphological hip classification system proposed by Robin et al.²¹

Table 4.1 Summary of 6 patients (Group A) treated with RF-DRG and systematically evaluated.

m/f	Age (yr)	Aet	GMFCS score	RF-DRG		Indication		Improv 4w			SE 4w		Improv 6m			SE 6m		Hip morphology	
				Left	Right	Spas	Pain	Care	Spas	Pain	Care	Spas	Pain	Care	Spas	Pain	Care	Left	Right
1 f	6	Asph	V	L1-2	L1-2	■		■	+			no	+				no	IV	III
2 f	12	Tr	V	L1-4	L1-4	■	■	■	+	+	+	no	+	+	+	+	no	III	I
3 f	16	Prem	V	-	L1-3	■	■			+	+	no		+	+	+	no	II	V
4 f	11	Asph	V	L2-4	L2-4	■			+			no	+				no	II	IV
5 m	7	Prem	V	L1-2	-	■				-		yes		+			no	V	III
6 f	14	Asph	V	-	L1-3	■	■	■	+	+	+	no	+	+	+	+	no	III	V

m: male; f: female; yr: years; spast: spasticity; Aet: Aetiology: Asph: Asphyxia; Tr: Trauma; Prem: Premature; SE: Side-effects; Improv: Improvement; 4w: 4 weeks; 6m: 6 months

■: indication

Improvement: +/-: summary of improvement/worsening measured by the self-made questionnaire

Table 4.2 Summary of 11 patients (Group B) treated with RF-DRG and evaluated by VAS.

m/f Age		SCPE GMFCS		RF-DRG-	RF-DRG-	Indication		VAS	Improvement		VAS	Δ-VAS	SE	Hip morphology		
(yr)		Score		left	right			pre			post					
						Spas	Pain Care		Spas	Pain	Care			Left	Right	
1 f	18	2	V	L1-3	-		■	8	+			2	6	no	III	V
2 f	22	2	V	L1-4	-	■	■	10	+	+		1.5	8.5	no	ns	ns
3 f	10	2	V	L1-2	L1-2	■	■	10	+			8	2	no	V	III
4 m	16	2	V	L1-3	-		■	7		+		3	4	no	II	V
5 m	16	2	V	L1-4	-	■	■	8.2		+		1.6	6.6	no	IV	V
6 m	7	2	V	-	L1-3	■		ns				ns		yes	0	III
7 m	5	2	V	L1-3	L1-3	■		ns			+	ns		no	IV	IV
8 f	11	2	V	L1-2	-		■	6		+		2	4	no	*	II
9 f	10	2	V	L1-2	-	■	■	8		+	+	5.5	2.5	no	I	I
	12	2	V	L1-2	-	■	■	8		+	+	5	3	no	I	I
	14	2	V	L1-2	-	■	■	10				10	0	no	I	I
10m	5	2	V	L1-4	L1-4	■		ns	+			ns		no	II	V
11f	16	2	V	L1-4	L1-4	■	■	8.7	+	+	+	3.1	5.6	no	ns	ns

m: male; f: female; yr: years; SCPE: surveillance for cerebral palsy in Europe classification: (1) unilateral; (2) bilateral * Osteomyelitis; ns: not scored; SE: Side-effects

■: indication

+: domain in which the improvement measured by VAS was noted

Six children (group A) were systematically evaluated at baseline, and 1 month and 6 months after treatment (table 4.1, table 4.3). In this group all assessments were performed by a physical therapist. The Modified Ashworth Scale (MAS) was used for the assessment of changes in muscle tone.²² In the MAS muscle tone is scored on a 6 point scale, in which “0” represents no hypertonia or no increase of muscle tone and “4” represents severe hypertonia and severe stiffness of the extremities. In each patient hip flexion and adduction, knee flexion and extension, and dorsal and plantar flexion in the ankle were tested bilaterally. Functional improvement was assessed using the Gross Motor Function Measure (GMFM), a widely used scale consisting of 5 different locomotor domains to evaluate treatment of spasticity in children with CP.^{23–25} Furthermore, we developed a more extensive questionnaire for caregivers. Besides items on pain, several items of daily activities of life, like dressing, undressing, and bathing, were investigated. Data of the 6 systematically evaluated children were statistically analyzed using a students T-test and a Wilcoxon signed rank test. A p value of < 0.05 was considered to be statistically significant. All data are represented as means and standard error of means (SEM).

Tabel 4.3 Ashworth scores of the first 6 patients: pre-operative, post-operative 4 weeks and 6 months

Pt		Hipflexion		Hip adduction		Knee flexion		Knee extension		Ankle dorsal flexion		Ankle plantar flexion	
		L	R	L	R	L	R	L	R	L	R	L	R
1	Pre	1+	1+	1	2	1	2	0	0	3	3	0	0
	Post4w	1	1	0	0	1	1	0	0	2	2	0	0
	Post6m	1	0	1	1	1	0	0	0	3	2	0	0
2	Pre	0	0	1	3	0	0	1	1	3	3	0	0
	Post4w	0	0	1	1	0	0	1	1	1	1	0	0
	Post6m	0	0	1	1	0	0	0	0	1	1	0	0
3	Pre	0	1	1+	2	1	1	2	2	3	3	0	1
	Post4w	0	1+	1+	1	1+	1	2	1+	2	2	0	0
	Post6m	2	1	2	1	2	1	0	0	2	2	0	0
4	Pre	0	0	1	1	1+	1+	3	3	0	0	1	1
	Post4w	0	0	0	0	2	2	0	0	1	0	0	0
	Post6m	1	1	0	0	2	2	0	0	1	1	0	0
5	Pre	2	0	0	1	0	1+	2	2	2	2	1+	1+
	Post4w	1	1	0	1	1	2	1	4	1	1	2	3
	Post6m	2	0	0	0	2	4	0	0	2	3	0	0
6	Pre	3	3	4	4	4	4	4	4	4	3	4	3
	Post4w	0	0	1	0	3	1	2	3	2	1+	2	2
	Post6m	3	3	4	3	3	3	0	0	4	4	4	4
Mean	Pre	1	0.83	1.33	2.17	1.17	1.5	2	2	2.5	2.33	1	1
	Post4w	0.33	0.5	0.75	0.5	1.33	1.17	1	1.5	1.5	1.17	1.67	0.83
	Post6m	1.5	0.83	1.33	1.0	1.67	1.67	0.17	0	2.17	2.17	0.67	0.67

The subsequent 11 children (group B) were evaluated at 6 weeks and 3 months using a Visual Analogue Scale (VAS; figure 4.1), which was used to measure the severity of the individually formulated problems. We changed the evaluation methods, as we were not able to detect the kind of change that the caregivers unanimously did notice. Furthermore, literature had become available which showed that the MAS and the GMFM are not indicated to measure changes in these severely handicapped children.²⁶⁻²⁸ Instead we used a VAS, which is a valid pain-rating instrument.²⁹ The VAS used in pain assessment is a straight 10 cm horizontal line with anchor points of no pain (score 0) and unbearable pain (score 10). For our study we changed the anchor points into very satisfied (score 0) and very dissatisfied (score 10) to use the VAS uniformly for individually defined problems.^{30, 31} A VAS score for spasticity, pain, and ease of care was given by the caregivers, since the majority of the patients with CP were severely mentally handicapped. Usually the patient and his/her caregiver(s) are the best judges of the severity of the impairments accompanying spasticity, as they are the only people who can assess its impact on the daily life of the patient.³² Caregivers of children with profound impairments note changes in function far more accurately than staff workers.³³

Figure 4.1 The VAS device

Score 0 / "geen": Very satisfied

Score 10 / "meest": Very dissatisfied

RF-DRG procedure

All patients were treated in our outpatient clinic, and RF-DRG was performed as described.^{12, 34} Under general anaesthesia, the patients were placed in prone position on an operating table. The level to be treated was based on clinical symptoms; afterwards stimulation was used to verify these levels.

The procedure was performed in tunnel vision, a technique for entering the electrode in the direct vision of the X-rays. Therefore, the C-arm (Ziehm electronics) was adjusted in such a way that the X-rays ran parallel to the end plates of the relevant level. Thereafter, the C-arm was rotated until the processus spinosus projected over the contralateral facet column. With the C-arm in this projection, the injection point was found by projecting a metal ruler over the lateral part of the foramen intervertebrale.

A 10-cm long, 22-G needle SMK-5 mm tip was inserted locally in the direction of the X-rays. Thereafter, the direction was corrected in such a way that the needle was being projected as a point on the screen. The direction of the radiation beam was now modified to a profile (lateral) view, and the needle was inserted until the point was located in the craniodorsal part of the foramen intervertebrale (Figure 4.2a).

Figure 4.2 Photomicrograph showing the position of a RF electrode a: lateral view and b: anterior-posterior view after injection of Omnipaque.

In an AP view, the course of a small amount of contrast agent was followed with “real-time imaging”; it should spread out laterocaudally along the spinal nerve (Figure 4.2b). The stylet was removed and exchanged for the radio frequent probe. After checking the impedance (an indicator for the type of tissue next to the cannula tip), electrical stimulation was started at a rate of 2 Hz and the corresponding muscles were observed for contractions. At 2 Hz stimulation motor contractions should be observed in the area of the relevant muscles at a threshold between 0.4 -0.8 Volts. 1 ml local anaesthetic solution (bupivacain 0.5%) was injected and radio frequent current was then led through the electrode in

order to increase the temperature to 67 °C for 60 seconds. Total operating time, including anaesthesia, was about 45 minutes. All patients were discharged from the clinic the same day after full recovery from the anaesthesia.

RESULTS

A total of 19 RF-DRG treatments were performed in 17 patients. One patient received three interventions, as the effects gradually wore off. A summary of the clinical data, including treated levels and outcome measures, are given in table 4.1 (group A: 6 patients) and table 4.2 (group B: 11 patients). In 2 patients a transient increase in pain after the RF-DRG procedure was noted, and 1 patient was successfully treated with Gabapentine for 4 weeks. No further side-effects (e.g. dysaesthesia or excessive weakness in the treated limbs) were reported. No significant differences were observed between the different lumbar levels for both the impedance and the stimulation threshold.

Group A: In the first six systematically evaluated children (table 4.1) an improvement in muscle tone after RF-DRG was detected on both the short (4 weeks) and long (6 months) term using the MAS. Especially the right hip adductors showed improvement on the MAS which went from 2.2 +/- 0.5 before RF-DRG to 0.5 +/- 0.2 four weeks after RF-DRG and 1.0 +/- 0.4 six months after RF-DRG (table 4.3). Due to the small sample size, no comment on the lack of significance of a null result can be given.

Using the GMFM no improvement was observed after RF-DRG treatment. At baseline a mean total score including all 5 domains of 17.2 % +/- 6 was found. After 4 weeks the score was 17.3 % +/- 7 and after 6 months the score was 16.2 % +/- 6.

Using the caregiver's questionnaire, an improvement in ease and quality of care and pain was detected. Although statistically not significant, in four patients pain in the lower extremities decreased, at both 4 weeks and 6 months. In one patient there was no change in pain and in another patient pain increased at 4 weeks but decreased at 6 months when compared to the baseline.

Group B: Because of the abovementioned results we switched to a VAS to evaluate the initiated treatment in the subsequent patients. This score was available in 8 out of the 11 patients. The missing values are due to the fact that some caregivers did not feel comfortable judging their own child in a numerical way. During outpatient follow up, the evaluation of the VAS scores showed improvement in most of the defined treatment goals in most children (table 4.2). Most parents reported that the positive effects of the RF-DRG lasted at least 6–9 months.

In one patient (no. 9), the VAS score showed no change after the third procedure. Her flexor spasms were then successfully treated with Botulinum Toxin-A injections in the iliopsoas and adductor muscles (Dysport, Ipsen).

DISCUSSION

To test our hypothesis that RF-DRG may be a serious treatment option for severe spasticity in children with CP, we undertook a pilot study in 17 patients. Our primary treatment goal was improvement of well-being and ease of care of patients with CP with severe hip flexor/adductor spasms and pain. Our first 6 consecutively treated patients (Group A) were evaluated at baseline, 1 month after treatment, and 6 months after treatment using the GMFM and the MAS. We found a small improvement in muscle tone on the MAS, but no effect on the GMFM scale. Despite this, the caregivers of these six treated children unanimously stated that the quality of life of their children had indeed improved after the RF-DRG (data not shown, summary represented by +/- in table 4.1). This disagreement between the MAS and the judgement of the caregivers highlights the difficulties measuring change in these severely handicapped children. The MAS as a method for the evaluation of the treatment of spasticity in children with CP has been disputed before, although in adult populations the reliability of the MAS has been demonstrated.²⁸ In a study in children with moderate to severe spasticity, a wide variability in test-retest results was reported for the MAS.²⁷ The assumption that the MAS exclusively measures spasticity is not entirely right. The MAS measures a broader set of neural and musculoskeletal factors of non-velocity-dependent hypertonia in addition to spasticity itself.²⁶

Furthermore, we added up the MAS scores of different muscles to produce a summed Ashworth score, in order to compare with most previous studies. However, this might be methodologically incorrect as the Ashworth score is an ordinal level measure.³⁵

For the next 11 patients we thus changed our evaluating system: instead of the MAS and the GMFM, we asked the caregivers to give a VAS score for spasticity, pain, and ease of care at different time points. Using this outcome measure we were able to show a significant improvement in spasticity, pain, and ease of care after an RF-DRG procedure, lasting up to 9 months. In two patients we found a transient increase in pain, for which 1 patient received Gabapentine for 4 weeks. This is a known transient procedure related event.³⁶ Although this was not a controlled study, the amount of improvement in VAS scores is in the same range as in conventional treatments, e.g. ITB and SDR.^{30, 37} RF-DRG is thus a promising new treatment option for severe spasticity in patients with CP, and its definitive effectiveness remains to be defined in a randomized controlled trial. It is less invasive and probably has less side-effects than ITB and SDR, but its main disadvantage in this patient population is, of course, the temporary character of its effects. In this regard RF-DRG resembles BTX-A treatment, but its main advantage over this therapeutic option is its strong pain-reducing effect. Theoretically, repetitive RF-DRGs may lead to dysesthesias and causalgias, but we have not seen this in the one patient we treated three times.³⁴ To prevent this possi-

ble side-effect, more definitive effects of RF-DRG might perhaps be achieved with higher radiofrequency currents and temperatures during the procedure.

Our pilot study does highlight the methodological problem of evaluating treatment effects in children with CP. As we were not able to conduct an extensive battery of clinical tests in our pilot study, we had to select a few outcome measures. Using the MAS and the GMFM, we were not able to detect any beneficial effects, which is in line with other studies.³² We had to resort to a VAS to find improvements in the condition of treated patients. In retrospect we should also have included the Pediatric Evaluation of Disability Inventory (PEDI), which is a generic standardized instrument used by the multidisciplinary team for evaluating functional performance, programme monitoring, documentation of functional development, and clinical decision-making.^{30, 37, 38}

The exact mechanism of action of an RF-DRG remains unknown. We recently reported an increase of proliferation inside the dorsal root ganglion after RF-DRG adjacent to the ganglion without signs of neural tissue damage (e.g. necrosis) inside the ganglion.³⁹ For years, the only mode of action of a radiofrequency lesion was thought to be through nerve damage due to thermocoagulation.⁴⁰ Recent experiments with pulsed radiofrequency treatment (a high-frequency current delivered in bursts of 20 ms followed by a silent period of 480 ms, during which the generated heat is washed out) suggest that thermocoagulation is not the only mode of action.^{40, 41} A late and temperature-independent increase in the expression of the immediate early *c-fos* gene within the rat spinal cord was found after exposure of the cervical dorsal root ganglion to continuous radiofrequency (67° C) and pulsed radiofrequency current.⁴² In one model of spasticity, the locomotor abnormalities are thought to be the result of hyperexcitability of spinal interneurons involved in the spinal stretch reflex.⁴³ Reduction of spinal input through de-afferentation is then the basic mechanism of RF-DRG.

CONCLUSION

Our pilot study on RF-DRG in 17 patients with CP with severe hip flexor/-adductor spasms and pain shows that it may improve spasticity, pain, and ease of care, with a duration of up to 9 months. As the amount of improvement is in the same range as in conventional treatments, RF-DRG is thus a promising new treatment option for severe spasticity in patients with CP, and its definitive effectiveness remains to be defined in a randomized controlled trial. The main advantages are the less invasive character of RF-DRG compared to the SDR with the potential benefit of a shorter hospitalization period, and its clear pain-reducing effect.

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CHAPTER V

LEVETIRACETAM THERAPY FOR TREATMENT OF CHOREOATHETOSIS IN DYSKINETIC CEREBRAL PALSY

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ABSTRACT

Dyskinetic cerebral palsy (CP) is a movement disorder that is difficult to treat and which causes major disability. We report on two female patients (aged 5 and 8 years) who experienced severe perinatal asphyxia and developed dyskinetic CP, clinically characterized by choreoathetosis.

Neuropsychological testing of these children showed a low average developmental quotient and no attentional deficits. Monotherapy with Levetiracetam (LEV) was initiated to improve balance control and fine motor skills. Treatment was evaluated by means of video analysis and the Visual Analogue Scale. In both children an impressive improvement of balance control and fine motor skills was observed. No side-effects occurred. Furthermore, both patients showed more interest for and pleasure during activities according to their parents. In a recent multidisciplinary evaluation of the initiated therapy, the parents, the therapist, and the rehabilitation doctor all confirmed that the effect initially observed was still present at 14 respectively 26 months after commencement of treatment. To our knowledge, this report on two patients with dyskinetic CP is the first suggesting that LEV may offer an alternative to the standard therapy of involuntary, uncontrolled movements in this group of patients.

BACKGROUND

Cerebral palsy (CP) is a non-progressive disorder of posture or movement caused by a lesion of the developing brain. The Surveillance of Cerebral Palsy in Europe (SCPE) has classified CP into three main groups (spastic, dyskinetic, and ataxic), which are based on clear neurological signs indicating pathology of the cerebral motor systems (table 1.1).¹ Dyskinetic CP presents with involuntary, uncontrolled, recurring, and, occasionally, stereotyped movements. The SCPE distinguishes between dystonic and choreoathetotic subtypes for dyskinetic CP. The pathophysiology of dyskinesia in CP is not fully elucidated, but existing evidence suggests that disorders of the basal ganglia (BG) play a role in this entity.

The symptomatic treatment of this movement disorder is still very difficult. In a retrospective survey of 22 children with extrapyramidal CP, only a minority showed a functional improvement using trihexyphenidyl, which is a centrally active muscarinic antagonist.²

Several anticonvulsants seem to be efficacious for the treatment of (paroxysmal) involuntary movement disorders. On the basis of a recent report about Levetiracetam (LEV) efficacy in the treatment of movement disorders, we started LEV in two patients with dyskinetic CP unresponsive to conventional drugs mostly used in such cases.³

To our knowledge, this report on two patients with dyskinetic CP, is the first suggesting that LEV may offer an alternative to standard therapy of involuntary, uncontrolled movements in this group of patients.

METHODS

Informed consent of the parents was obtained for both patients. LEV was only started after the other available drugs usually prescribed had failed. Baclofen (GABA-agonist) and Artane (Muscarine-antagonist) were tried but did not show the desired effect. The initial dose of LEV was 2.5mg/kg/day. The dosage was titrated over weeks to months, based on response as well as tolerability.

Cognitive functioning of both children was described using standardized instruments which could be used in children with serious disabilities, as formal testing with, for instance, the Wechsler Intelligence Scale for Children-III is not possible because of motor disabilities.⁴ We used the Peabody Picture Vocabulary Test - Third Edition (PPVT-III-NL)⁵ to describe receptive vocabulary, which is a commonly used screening test for verbal ability. Furthermore, a subtest from a standardized Dutch nonverbal intelligence test (subtest matrix analogies from the Snijders Oomen Nonverbal Intelligence Test)⁶ for which no motor response is necessary, was used. Using the Child Behavior Checklist (CBCL), which is a by-

proxy instrument, general behavioural functioning, especially the existence of attentional problems, was assessed.⁷

The patients were re-evaluated on a regular basis by an occupational therapist, using video analysis. The parents regularly used the Visual Analogue Scale (VAS), an ordinal scale that ranges from 0 to 10, to score improvements on goals defined before treatment with LEV was started. The VAS is known as a valid and reliable measure for rating pain intensity in adults and children of more than 6 years of age and has recently been found useful for evaluating therapy in children with CP.^{8, 9} When clinicians are raters, the VAS validly identifies the minimal clinically important difference on the Pediatric Evaluation of Disability Inventory.¹⁰

Based on these two parameters combined with regular visits at our outpatient department (LS and JSHV) a decision was made with the parents either to continue the drug or taper it off.

Case 1

A 5-year-old female experienced severe perinatal asphyxia (umbilical artery pH 6.8). Pregnancy had been complicated by pre-eclampsia. Neurological examination was compatible with Sarnat II encephalopathy. During the first hours of life the infant experienced severe neonatal seizures, for which she was treated with midazolam. The electroencephalogram showed a burst suppression image with severe epileptic activity. MRI showed abnormal signal intensity within the basal ganglia and thalami. Furthermore, focal signal abnormalities in the posterior limb of the internal capsules were observed.

From the beginning, she showed developmental delay and hypotonia. As time went by she developed a severe movement disorder characterized by involuntary, uncontrolled, and occasional stereotyped movements, which can be classified as dyskinetic CP. Psychological examination showed that her vocabulary quotient on the PPVT-III-NL was low average (quotient score 82). Matrix reasoning was in accordance with this level of verbal abilities (standard-score 85). Her behaviour (reported by the parents using the CBCL) did not reveal significant attentional problems.

At the age of 5 years she was presented to the outpatient clinic for further treatment. The following goals were formulated: to improve sitting independently (balance control) and to improve grasping for and pointing towards objects (fine motor skills). Monotherapy with LEV was initiated, reaching a final dose of 5mg/kg/day. Raising this dose was suggested, but parents were satisfied since all the treatment goals were achieved.

Evaluation of therapy and obtainment of VAS scores were carried out on a regular basis. After 3 months the child's parents rated her balance control limitations as 0 (before treatment: 8.2) and her limitations concerning grasping and fine motor skills as 3 (before treatment: 8.2). The patient is, for the first time in

her life, able to drink independently from a cup with two handles. Also, she is now able to bring a fork to her mouth after being handed the fork and she needs less assistance when colouring. The patient shows more initiative and pleasure during activities has increased according to her parents. At 6, 9, and 14 months after commencement of treatment VAS scores confirmed these improvements.

Comparing videos before LEV treatment and 3 months after initiating medication, fewer fidgety movements of the trunk, less overextension of arms and hands during actions, and less (dystonic) co-movements of arms and mouth were seen. To our surprise she also showed marked improvement of speech and was now easier to understand. This was confirmed by a speech therapist. No side-effects were noted.

In a recent multidisciplinary evaluation of the initiated therapy, the parents, the therapist, and the rehabilitation doctor all confirmed that the effect initially observed was still present 14 months later.

Case 2

An 8-year-old female was born by means of Ventouse delivery after normal pregnancy. She was suffering from severe periparturient asphyxia (pH 7.12) and had to be resuscitated.

From the beginning she showed developmental delay, axial hypotonia, constant abnormal tongue protrusion, and abnormal spontaneous motor activity. At the age of 7 years she was re-evaluated. Neurological examination showed a cooperative child with good social contact, but with a severe dyskinetic movement disorder, which, for example, made reaching for objects impossible. Furthermore, an MRI was performed and showed abnormal signal intensity within the lateral thalami and in the dorsal putamen on both sides.

Psychological examination showed that her vocabulary quotient on the PPVT-III-NL was in the low average range (quotient score 80). Her matrix reasoning was also low average (standard-score 78). CBCL behaviour report by the parents and teachers did not reveal significant attentional problems.

Therapy with LEV was initiated to improve trunk balance and fine motor skills. The starting dose was 2.5mg/kg/day and was titrated to a final dose of 10mg/kg/day. No side-effects were noted.

Evaluation of therapy and obtainment of VAS scores were carried out on a regular basis. After 6 months, parents rated her balance control limitations as 5 (before treatment: 7) and her fine motor skills limitations as 6 (before treatment: 10). Again, the patient showed more interest in and pleasure during activities according to her parents.

Comparing videos before medication and 3 months after initiating medication one can see that she is now able to independently cut pieces of paper whereas before much assistance was needed. Both the number of uncontrolled movements and their ranges of motion decreased.

The child is now capable of holding a pencil with just three fingers and staying between the lines while previously she used her whole hand just to draw several uncontrolled crude lines. While working on her computer she used to be able to click on a 5cm square, but this has now decreased to a 2cm square.

In a recent multidisciplinary evaluation of the initiated LEV therapy, the parents, the therapist, and the rehabilitation doctor all confirmed that the effect initially observed was still present 26 months later.

DISCUSSION

The main difficulties for patients with choreoathetoid CP relate to their involuntary movements, which can be very powerful and extremely difficult to interrupt, making purposeful movement impossible.¹¹ In patients with Huntington disease, it was found that chorea, when moderate to severe, can cause major disability and have a significant negative impact on daily life.¹² In Parkinson patients, it was found that dyskinesias are associated with a reduction of Quality of Life and with an increase in total health-related-costs.¹³ In children with choreoathetoid encephalopathy after cardiac surgery, it was found that restrictions in the range of activities in which children participated (e.g. hobbies, clubs, sports) and difficulties in peer and sibling relationships led to poor total adaptive competence.¹⁴

So one may conclude that choreoathetosis is a very disabling disease. Various drugs have been tried but with no great success. We did not try the recommended presynaptic and postsynaptic dopamine antagonists because of lack of experience. Furthermore, tetrabenazine is not available for the treatment of children in the Netherlands.

To our knowledge, this is the first description of two patients with a non-progressive, non-paroxysmal, dyskinetic movement disorder who have been treated with LEV to diminish choreoathetosis.

Evaluation of LEV treatment was done both objectively, by video analysis, and subjectively, by VAS. After 6 months both video analysis and VAS showed that (limitations by) choreoathetosis had decreased while no side-effects had occurred. It is very unlikely that these positive effects are due to maturation or to training given the course over time. Reasons for not increasing the dose of medication any further were that parents felt that all the goals were accomplished and that adverse affects, like somnolence, obtundation, and Parkinsonism, of which they were informed beforehand, should be avoided.^{15, 16}

Based on the results achieved with these two patients we may conclude that LEV may be used as an alternative to treat unmanageable choreoathetosis of a non-progressive kind, e.g. in children with dyskinetic CP. This is important because choreoathetosis appears to be a very severe and disabling condition which is difficult to treat. This could partly be due to the differences in patho-

physiology between the two aspects of the condition, i.e. athetosis can be treated by increasing dopaminergic activity in the BG, while chorea can be treated by decreasing dopaminergic activity.²

These findings and our results suggest that LEV might reduce choreoathetosis by means of another pathway. So far, the synaptic vesicle protein SV2A has been identified as the binding site for LEV, but the molecular action of SV2A is still unknown.¹⁷

Further and larger studies are needed to confirm the positive effects of LEV on choreo-athetosis in patients with a non-progressive, non-paroxysmal, dyskinetic movement disorder.

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CHAPTER VI
VISUAL ANALOGUE SCALE TO SCORE THE
EFFECTS OF BOTULINUM TOXIN A
TREATMENT IN CHILDREN WITH CEREBRAL
PALSY IN DAILY CLINICAL PRACTICE

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ABSTRACT

Objective

This study examined the validity and efficacy of the Visual Analogue Scale (VAS) when evaluating spasticity treatment in an outpatient setting.

Patients and methods

We used a parent-reported VAS device to evaluate the effects of Botulinum Toxin A (BTX-A) treatment. Data were collected on 55 children with cerebral palsy (CP). Individual goals of treatment were formulated in close consultation with the caregivers. The categories of treatment options were improvement of pain, problems with nursing, sitting position, standing, and walking.

Results

Seventy-four interventions were performed in 55 children with CP. A statistically significant effect was found for improvement of nursing, standing, and walking. No statistically significant effect for pain was found, probably because of small numbers. In seven children there was no effect at all. Side-effects were observed in five children. A positive (not significant) correlation was found between the VAS and the Modified Tardieu for those children who also underwent gait analysis.

Conclusion

Using a VAS device, beneficial effects were found for nursing, standing, and walking after BTX-A treatment. Evaluating spasticity treatment by use of the VAS has important advantages as it is a quick and easy method for evaluating individually defined treatment goals in an outpatient setting, in which time-consuming evaluations are not an option.

INTRODUCTION

Cerebral palsy (CP) is the most common cause of childhood physical disability. Its clinical presentation can be very diverse, although 70–80% of the patients have spastic clinical features.¹

Spasticity is a motor disorder characterized by a velocity-dependent increase in muscle tone with exaggerated tendon jerks.² Several studies have shown the benefits of intramuscular Botulinum Toxin Type A (BTX-A) injections for the management of spasticity in children with CP.^{3–5} Studies indicate that parents of children with CP consider BTX-A treatment to be an acceptable form of therapy.⁶

BTX-A inhibits cholinergic transmission at neuromuscular synapses and relaxes muscles. Clinical effects are usually observed after 2–5 days and last for 16–24 weeks.^{7–9} Although evaluation of therapy is essential, there is no quick and easy to use outcome measure available to evaluate the effects of BTX-A injections in spastic children in daily clinical practice. In spite of its clear limitations, the standard clinical scale for measuring spasticity at function level of the International Classification of Functioning, Disability, and Health (ICF, WHO 2001) is the Ashworth Scale.¹⁰ However, the Ashworth Scale does not measure spasticity exclusively, it has low inter-rater reliability, and it lacks precision and sensitivity for measuring smaller changes in spasticity.^{11–13}

Although the Gross Motor Function Measurement (GMFM) is widely accepted as the best available quantitative measure for gross motor function in CP at activity level of the ICF, it is of limited value when determining functional benefits in severely affected children.¹⁴

In our outpatient clinic patients with different degrees of severity of CP are seen. Goals for BTX-A treatment are defined together with parents or caregivers and the children themselves. To quantify their satisfaction in functioning within these goals, a Visual Analogue Scale (VAS) is used. This is a subjective measure in which caregivers or children themselves are able to assess their level of functioning with regard to sitting, standing, and walking (activity level of the ICF). In more severely affected patients pain or ease of caregiving can be rated with the VAS. In ICF terms, this will influence participation and quality of life.

In this article, the results of BTX-A injections on nursing, sitting, standing, walking, and pain in a group of children with CP as evaluated by means of the VAS are presented. Furthermore, correlations will be made between the VAS, a subjective measure, and more objective measures at function level of the ICF in patients able to walk.

PATIENTS AND METHODS

In order to evaluate our daily clinical practice, we prospectively collected data on 55 children with CP (25 males; 30 females) with a mean age of 8.3 years (SD 3.3) at the moment of the first intervention (table 6.1). Patients were carefully selected for BTX-A treatment by a multidisciplinary team of specialists (LR, LS, JV, and physiotherapists). Depending on the individually formulated goals the target muscle groups for treatment were defined. The treatment goals are shown in table 6.2. Children were included for treatment only after informed consent of the caregivers.

Table 6.2 Defined intervention goals

	GMFCS	Walking	Pain	Nursing	Standing
Diagnosis					
Unilateral	1	12	1	-	2
	3	1	-	-	-
Bilateral	1	6	1	-	-
	2	11	-	-	-
	3	14	-	5	4
	4	11*	1	6	4
	5		1	13	5

* Indoor walking and transfer

Intervention

The children received BTX-A injections (Dysport, Ipsen) under general anaesthesia in the day-care department of the Maastricht University Medical Centre (LR, LS, and JV). Each patient was given an individual clinical examination in order to determine which muscles to inject. Spastic hypertonia of a specific muscle disturbing strength and/or function or causing pain or difficulty in caregiving was a criterion to inject. The target muscles were located with the help of electrical stimulation.

Maximum dosage: 23 MU/kg bodyweight, limited to no more than 400 units per limb, within an overall maximum dose of 1200 MU per session. After treatment, all children were discharged on the same day and they continued with their physical therapy. They were followed up at the outpatient clinic 6 and 12 weeks after intervention.

Outcome measures

Individual goals of treatment were formulated in close consultation with the caregivers. The categories of treatment goals were improvement of pain, problems with nursing, sitting position, standing, and walking.

The VAS was used to measure the severity of the individually formulated problems. The VAS is a valid and reliable measure in rating pain intensity.¹⁵ The VAS used in pain assessment is a straight 10cm horizontal line with anchor points of no pain (score 0) and unbearable pain (score 10). We changed the anchor points into very satisfied (score 0) and very dissatisfied (score 10) in order to use the VAS uniformly for the individually defined problems. On the day of the intervention, one of the authors (LS or JV) asked the caregivers to define their goal of the treatment and to assess their VAS score. The instrument used to rate the VAS score is shown in figure 6.1.

Figure 6.1 The VAS device

'Geen' = very satisfied (score 0), 'Meest' = very dissatisfied (score 10).

We correlated the VAS with a Passive Range Of Motion (PROM), Angle Of Catch (AOC) and the Modified Tardieu for children who were able to walk.

Follow-up of each child took place at 6 and 12 weeks after intervention and a VAS score was rated. For statistical analysis the most improved post-treatment VAS score was used.

The caregivers were not informed about their pre-treatment score. Furthermore, information about side-effects and complications was collected.

Statistical analysis

The data were analyzed using SPSS 11.0.1. We used a paired sample t-test to compare the pre- and post-treatment VAS scores. One-way Anova was used to analyze sex differences affecting the dependent measures caregiving, standing, walking, and pain perception. One-way Anova was also used to test differences in aetiology and type of CP related to the effect of intervention on dependent measures. In order to calculate the correlations between the VAS and the PROM, AOC, and Modified Tardieu, we used the Spearman's rho.

Table 6.1 Clinical characteristics of the children included in the study

Patient	Treat #	Sex	Age (years)	SCPE	GMFCS	# Muscles	Total dose (MU)	Weight (Kg)	VAS Pain		VAS Care		VAS Standing		VAS Walking	
									Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	1	F	18	2	1	6	550	70	9.4	0					7.3	0
2	1	F	9	2	5	4	435	28			7	3				
	2		10			4	435	32			7.6	4.3				
3	1	M	13	2	1	1	200	9							7	4
4	1	F	14	2	2	6	800	35							6	2
5	1	M	14	2	1	10	560	30							10	0
	2		15			10	820	34							10	0
6	1	M	12	2	2	6	1000	37							8	5
7	1	F	14	1	1	1	200	9							8	3
8	1	F	12	2	4	6	720	29							7	3
	2		13			8	975	31							8.9	2.8
9	1	F	14	2	2	4	350	38							6.6	7.6
10	1	M	14	2	4	6	900	30			6	3	6	3	6	3
11	1	M	11	2	3	6	800	48							7	4
12	1	F	11	1	1	2	500	48							5	5
13	1	M	10	2	2	8	370	33							8	2
	2		11			7	950	35							8	2
14	1	M	13	2	3	8	800	42							8.5	2
15	1	M	12	2	5	8	700	31			6.7	4.6	7.7	5.2		
16	1	M	10	2	3	8	450	15			5	2			5	2
17	1	M	7	2	4	8	500	17			6	3			6	3
	2		10			10	600	24							5	1.3
3			11			10	600	25			5	2			4	2.8
4			12			10	600	30			4	2.8			6	2.8
18	1	F	8	2	2	8	660	29			6				7	3
19	1	F	11	2	4	8	800	24							7.5	1

Patient	Treat #	Sex	Age (years)	SCPE	GMFCS	# Muscles	Total dose (MU)	Weight (Kg)	VAS Pain		VAS Care		VAS Standing		VAS Walking	
									Pre	Post	Pre	Post	Pre	Post	Pre	Post
20	1	F	10	2	5	8	600	26	7.4	7.4	7.4	1.8	7.4	2.1		
21	1	F	10	2	5	2	200	19					6	2		
22	2		11			8	480	22			6	2				
22	1	M	8	2	5	6	300	20			5	2	10	4		
22	2		10			8	400	21			5	3.6	7.5	3.6		
23	1	F	10	1	1	3	350	15							7.9	5.5
24	1	M	8	2	3	7	380	17			7.0	4			7	4
25	1	F	7	1	1	2	350	33							8	5
26	1	M	8	2	3	6	450	19			7.9	4.8	8	4.4	6	2.3
26	2		10			7	500	22							8	4.7
27	1	F	7	1	1	4	300	25							7	3
28	1	M	7	2	5	7	600	23								
28	2		10			6	650	27			9.8	0.2				
29	1	M	5	2	4	10	550	24					5	2		
30	1	F	10	2	3	5	800	34							9	6.2
31	1	F	6	2	5	10	500	19			9	4				
31	2		8			2	150	27			8.8	1.3				
32	1	F	9	2	3	8	475	23							7	3
33	1	M	7	1	1	2	250	11							5	3
34	1	M	6	2	4	8	640	21					9	7		
34	2		8			8	650	28			6.8	3.7			6.8	3.7
35	1	F	7	2	1	3	400	19							5	3
35	2		9			2	250	24							5.5	3.5
36	1	M	6	1	1	3	330	14					2.2	0.8	2.2	0.8
37	1	F	6	2	2	8	600	26							5	5
38	1	M	6	1	1	1	200	23							5	5
39	1	F	7	2	3	2	350	20							7.3	2.6

Patient	Treat #	Sex	Age (years)	SCPE	GMFCS	# Muscles	Total dose (MU)	Weight (Kg)	VAS Pain		VAS Care		VAS Standing		VAS Walking	
									Pre	Post	Pre	Post	Pre	Post	Pre	Post
2	2		8			2	350	20							8	4
40	1	M	7	2	2	5	400	21							7.7	3
41	1	F	6	1	1	1	200	9							6	3
42	1	F	6	1	1	2	240	20							5	5
43	1	M	5	2	3	10	600	20							5	3
44	1	M	6	2	3	9	550	24							5	5
45	1	F	5	2	3	8	520	17							6	4
2	2		7			6	525	23					6	4		
46	1	F	4	2	2	4	500	20							7	5
47	1	F	3	2	4	8	450	11					8.1	2.4	8.1	3.2
2	2		7			8	450	18	5.5	2.7					6.2	4
48	1	M	4	1	1	2	160	14							5	2
49	1	F	7	1	3	2	225	21							6	4
50	1	F	5	2	2	6	410	18							6	3.5
51	1	F	7	2	3	3	375	20							4.5	2.5
52	1	F	4	2	3	6	330	16			4.9	4.9	8.6	1.8	10	1.2
2	2		4			7	440	18					7.9	2	7.8	3.2
53	1	M	5	2	3	8	400	15			8.5	4				
54	1	F	4	1	1	2	225	18					4	4	4	6
55	1	M	3	2	5	4	300	11	4	2	6	1				
2	2		4			5	275	12			7	2				

M: Male; F: Female; SCPE: Surveillance for Cerebral Palsy in Europe classification: (1): unilateral; (2): bilateral

RESULTS

Seventy-four interventions were performed in 55 children. In tables 6.1 and 6.3, the main clinical characteristics of the children included are shown. The mean age at the first intervention was for both girls and boys 8.3 years. Most of the children treated were premature born children (32 out of 55) with bilateral spastic CP (29 out of 32).

Table 6.3 Diagnosis, GMFCS, aetiology and sex of the treated population

		Aetiology						Total
		Premature		Asphyxia		Other		
		Male	Female	Male	Female	Male	Female	
Diagnosis								
Unilateral	1	1	2		1	3	5	12
	3						1	1
Bilateral	1	2	1				1	4
	2	2	4	1	1		1	9
	3	7	6			1		14
	4	3	3			1		7
	5	1		2	3	1	1	8
	Total	16	16	3	5	6	9	55

The number of interventions, the number of muscles treated, and the total dose of BTX-A used are shown in table 6.1.

Most interventions were bilateral (60 out of 74) and multilevel (50 out of 74). In some children, more than one goal was formulated by the caregivers. The most frequently formulated goal was improvement of walking (56 times), followed by nursing (24 times) and standing (15 times). Improvement of pain as an initial goal was formulated only 4 times.

In table 6.4 the results of a paired sample t-test are shown, comparing pre- and post-treatment related to the outcome variables. A statistically significant effect is found for improvement of care ($p \leq 0.000$), standing ($p \leq 0.000$), and walking ($p \leq 0.000$). No statistically significant effect is found for pain ($p = 0.180$) probably because of small numbers.

Table 6.4 Mean, standard deviation and significance comparing pre- and post treatment VAS scores on the variables caregiving, standing, walking and pain

Variable	N	Pre-treatment		Post-treatment		Difference		t-value
		Mean	SD	Mean	SD	Mean	SD	
Walking	56	6.62	1.61	3.27	1.56	3.35	2.41	10.40***
Pain	4	6.58	2.34	3.03	3.13	3.55	4.07	1.74 ^{n.s.}
Care	24	6.68	1.50	3.12	1.63	3.57	2.13	8.22***
Standing	15	6.89	2.04	3.22	1.60	3.67	1.96	7.27***

^{n.s.} not significant; * $p < 0.05$; ** $P < 0.01$; *** $p < 0.001$

Using an one-way Anova no statistically significant sex differences were found in treatment effect: boys reacted the same as girls to the outcome variables. Furthermore, no significant differences were observed between aetiology (pre-term birth versus term asphyxia). Statistical analysis comparing diagnostic groups (unilateral versus bilateral spastic CP) on the outcome variables could not be performed because of the small number of cases.

In table 6.5, the Spearman correlations between VAS scores (walking) and three clinical examinations of tone (PROM, AOC, and the Modified Tardieu) are presented. The following muscles were tested: quadriceps femoris, hamstrings, soleus, and gastrocnemius. In most cases, interventions were mainly restricted to gastrocnemius and hamstrings. Therefore, only these data could be analyzed. As we expected a positive relationship, an one-tailed test was used. Both PROM and AOC are not significantly correlated to the VAS. The VAS was positively correlated to the PROM for both muscle groups and to the AOC for the hamstrings. There was a negative correlation between the VAS and the AOC of the gastrocnemius. The Modified Tardieu was positively related to the VAS for all muscles investigated and significant for the left gastrocnemius.

Table 6.5 Spearman non-parametric correlation coefficient between VAS and PROM, AOC and Tardieu for walkers with a gait analysis

	N	ΔPROM	ΔAOC	ΔTardieu
Gastrocnemius				
Left	19	0.15 ^{n.s.}	-0.03 ^{n.s.}	0.39*
Right	22	0.03 ^{n.s.}	-0.14 ^{n.s.}	0.20 ^{n.s.}
Hamstring				
Left	15	0.22 ^{n.s.}	0.12 ^{n.s.}	0.18 ^{n.s.}
Right	18	0.24 ^{n.s.}	0.13 ^{n.s.}	0.07 ^{n.s.}

Δ : difference PROM, AOC and Tardieu (before and after treatment); PROM: passive range of motion; AOC: angle of catch; ^{n.s.} : not significant; * $p < 0.05$; ** $P < 0.01$; *** $p < 0.001$

In seven children (12.7%) there was no effect at all. Side-effects were observed 7 times in five children. One infant suffered from a flu-like illness and three had gastro-intestinal complaints: diarrhea (2) and constipation (1). In two children walking worsened and one child showed more instability during standing. In 36

of the 74 (48.6%), interventions a positive effect was observed for more than 12 weeks.

DISCUSSION

We evaluated the effect of BTX-A treatment on spasticity in children with CP in our outpatient clinic. Using a VAS device we found a beneficial effect on nursing, standing, and walking after BTX-A treatment. In previous studies, the beneficial effect of BTX-A treatment on pain and function has been demonstrated.³⁻⁵ The effect of BTX-A on walking is not clear. In the Cochrane review of Ade-Hall no significant effect was found.¹⁶ In articles in which parental satisfaction with functional ability was measured, positive effects are reported.^{17, 18} The results in our study concur with the above mentioned studies.

The main problem in studies evaluating spasticity treatment is the assessment of spasticity.

In a recent Cochrane review of anti-spastic agents for multiple sclerosis, the reviewers describe both the understanding of the pathophysiology and the ability to measure spasticity as seriously deficient.¹⁹

The Ashworth Scale still is the golden standard for evaluating spasticity treatment today.¹⁰ The Ashworth Scale as a method for the evaluation of spasticity has been disputed before, although in adult populations the reliability of the Ashworth Scale has been demonstrated.²⁰ In a study in children with moderate to severe spasticity, a wide variability in test-retest results was reported for the Ashworth Scale.²¹ Furthermore, the Ashworth Scale does not comply with the concept of spasticity, i.e. a velocity-dependent increase in muscle tone.¹³

In our study, we did not routinely use the Ashworth Scale for the assessment of the treated children because of the above mentioned reasons.

For measuring gross motor function in CP, the GMFM is widely accepted as the best available quantitative method. However, it is of limited value when determining functional benefits in severely affected children.¹⁴

The Tardieu Scale (TS) is a very comprehensive, but very time-consuming method to assess patients. Therefore its feasibility is questioned, especially for use in children.¹³ The 'dynamic component' is a measure derived from the TS and is a clinical measure of spasticity according to the literature.¹⁷ It can be calculated as the difference between the PROM at a very slow passive stretch and the AOC at a fast velocity stretch. However, it has been shown that the calculated difference adds together the variances of both joint angles, resulting in very wide inter-session variations.²² Therefore, it is probably better to compare the PROM and the AOC separately before and after treatment.¹³

Table 6.5 shows the correlations of the differences found with PROM, AOC, and the dynamic component with the differences found with the VAS. Although a positive correlation was found most of the time, it is clear that there is a sub-

stantial difference between the currently used standards for evaluating spasticity and the VAS which measures the impact of the treatment on the daily life of the patient and caregiver.

The VAS is a valid and reliable measure for rating pain intensity in adults and children over 6 years of age.¹⁵ In adults it has also been used for measuring satisfaction, feelings, quality of sleep, dyspnea, emotional function, fatigue and appeared to be responsive and valid.²³⁻²⁶ In pediatric patients, aged 5-17 years, the VAS has also been applied to measure anxiety, sadness, anger, worry, happiness, and fatigue.^{27, 28} The VAS showed preliminary reliability and validity for both child self-report and parent-proxy report.²⁸ When clinicians are raters, the VAS validly identifies the minimal clinically important difference on the Pediatric Evaluation of Disability Inventory.²⁹

Evaluating spasticity treatment with the use of the VAS has several important advantages. First, it is a quick and easy method for evaluating treatment in an outpatient setting, in which time-consuming evaluations are not an option and where there is a need for such an instrument.¹¹ Secondly, it is a subjective measure of the effects that BTX-A treatment has had on individually chosen goals. Usually the patient and his/her caregiver(s) are the best judges of the severity of the spasticity, as they are the only people who can assess its impact on the daily life of the patient.³⁰ It is known that caregivers of children with profound impairments note changes in function far more accurately than staff workers.³¹

In spasticity after a spinal cord injury, it has been recommended to use both the VAS and other clinical evaluation methods (Modified Ashworth Scale) before starting therapeutically interventions.³² Another method for outcome measurement is Goal Attainment Scaling (GAS), introduced in the late 60's by Kiresuk and Sherman.³³ An individual goal scale for each patient is developed during an interview. Outcome is measured on a 5-point scale. The GAS can be administered by unqualified persons, nevertheless some training is advocated. Although the GAS is found to be an appropriate scale for the evaluation of outcome after intervention, the scale development time (first goal setting) is estimated at 45 minutes.^{34, 35} In a busy outpatient clinic the scale development time of the GAS is at a clear disadvantage compared to the quick assessment with the VAS used in our study. Possibly, a further study could be set up to correlate the VAS with the GAS.

Our study results show that the VAS, although subjective, is a valid, easy, and quick method for evaluating spasticity treatment in an outpatient setting.

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CHAPTER VII

CONSTIPATION AFTER BOTULINUM TOXIN-A INJECTIONS IN LOWER AND UPPER LIMB MUSCLES:

**A transitory systemic autonomic adverse
effect. Report of three cases.**

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ABSTRACT

We report three patients who developed transient constipation after receiving therapeutic doses of Botulinum Toxin-A (BTX-A) for spasticity of the lower limbs (two cases) and the upper limb (one case). Constipation was observed within the first week after treatment. In all three cases, this symptom resolved completely and almost simultaneously with disappearance of the therapeutic effects of BTX-A. None of the patients had previously received BTX-A injections. Two patients received a second treatment and both presented the same autonomic cholinergic remote symptoms. The third patient refused a second treatment due to the complication noted earlier. Familiarity with this autonomic systemic side-effect of BTX-A is essential for those who treat patients already at risk for gastro-intestinal dysfunction. Because the adverse effects were treatable and transitory, we believe that constipation per se is not an absolute contraindication, if from a therapeutic point of view, BTX-A is indicated.

INTRODUCTION

In the past 20 years, Botulinum Toxin-A (BTX-A) has been used for a wide spectrum of therapeutic and cosmetic indications, whether or not approved by the Food and Drug Administration (FDA).¹ One of such indications not approved by the FDA, but widely studied and reported in the medical literature, is spasticity due to cerebral palsy (CP)²⁻⁴ or due to acquired brain injury.⁵⁻⁷

BTX-A prevents presynaptic release of acetylcholine at the neuromuscular junction and as a result chemodenervation develops in the injected muscle.^{8, 9} The toxin, in therapeutic doses, is considered to be effective and safe. Remote adverse effects are rare and include flu-like symptoms, anaphylactic reactions, and excessive fatigue.¹⁰ Nevertheless, treatment of spasticity due to CP with BTX-A can be limited by the escape of the toxin from the muscle causing local and distant side-effects.

We report three cases of patients suffering from severe spasticity, who repeatedly experienced a period of constipation as an important and disabling systemic autonomic cholinergic side-effect after BTX-A treatment for spasticity.

Case 1

An eleven-year old boy, suffering from spasticity and epilepsy due to CP, was referred to the outpatient clinic because of impaired mobility and nursing problems. Clinical examination showed a severely mentally handicapped boy, who was able to assist while being transferred from bed to wheelchair and even to make some steps if supported. Furthermore, body hygiene and dressing were hindered by hip adductor spasms. The possibility of treating the patient with BTX-A injections was discussed with his parents, and the following treatment goals were defined: to facilitate nursing and to improve mobility.

We determined the muscles to be injected by clinical examination. Spastic hypertonia of a specific muscle leading to functional limitations was the criterion to inject.

Therapy was initiated with informed consent of the parents. The child received BTX-A injections under general anaesthesia in the day-care department (JV). The target muscles were identified by muscular electrical stimulation. Dysport® from Ipsen was used according to the recommended maximum dosage: 23 IU/kg bodyweight, limited to no more than 400 units per limb, within an overall maximum dose of 1200 IU per session, with a dilution of 500 units in 2 ml NaCl 0.9%. The child's bodyweight was 25 kg. The adductor longus, semitendinosus, semimembranosus, and soleus muscles were injected with 50 IU of Dysport® each, and the gastrocnemius muscles with 100 IU (total dose 600 IU).

The patient was seen at our outpatient clinic at 6 and 12 weeks after the intervention. We evaluated the effects and side-effects by means of a standardised questionnaire. Caregivers had to fill out a list with all side-effects possible. The

Visual Analogue Scale (VAS), an ordinal scale that ranges from 0–10 with 0 being the optimal situation and 10 the worst situation, was also used to evaluate the intervention.¹² During follow-up, the mother observed an improvement on mobility (pre-treatment VAS: 5, post-treatment VAS: 1.3) and on facilitation in nursing (pre-treatment VAS: 4, post-treatment VAS: 2.2). However, as a remarkable side-effect she reported severe constipation, starting 4 days after the treatment, for which medication (macrogolum) was necessary.

The positive effects on mobility and nursing facilities lasted for more than 3 months and with lessening of these positive effects, the gastro-intestinal dysfunction wore off. After 4,5 months the clinical therapeutic effect was no longer detectable and at the same time macrogolum could be withdrawn.

One year after the first intervention there was a new request for repeated treatment because of increasing nursing and mobility problems. After a careful examination and discussing the systemic side-effect of constipation observed the first time, a decision was made to repeat the initial treatment. Under the same conditions and with a bodyweight of 30 kg, the same muscles were injected with the same dose. The defined goals were reached but the same systemic gastro-intestinal side-effect of constipation was observed. Again, as the positive effects on mobility and nursing diminished, the side-effect faded away.

Case 2

This 19-year-old male was admitted to the rehabilitation department four months after a severe head trauma with diffuse axonal injury leading to impairments of his cognitive functions, speech, and locomotion. At admission the patient presented a tetraplegia with generalized spasticity (Modified Ashworth Scale - MAS - 2 and 3) of upper and lower limbs, accompanied by a severe diminished range of motion of the knee and ankle joints bilaterally. Orthotic treatment was initiated. The patient was unable to stand and walk and was dependent for all transfers. During the rehabilitation program he eventually developed painful spasms in both legs. Oral spasmolytic medication (Baclofen and Tizanidine) at maximal therapeutic doses was insufficient. Treatment with BTX-A was then discussed and the patient and his parents gave informed consent. He had never been treated with BTX-A before.

One month after admission, the patient received his first BTX-A injection (Botox® from Allergan). The semitendinosus, the semimembranosus, and the biceps femoris muscles of the left leg were treated with 100 units of Botox® each; 300 units in total (maximum recommended doses by the manufacturer: 600 units) in a dilution of 100 units in 5 ml NaCl 0.9%. Approximately 6 days after the injections a significant reduction of the muscle tone of the left leg was observed. The painful spasms disappeared. About 10 days after the treatment the patient reported severe constipation accompanied by abdominal pain. Treatment with laxatives (Bisacodyl and lactulose) was necessary. After two

months, the intestinal function improved and at the same time the therapeutic effect of BTX-A diminished, although the range of motion could be maintained with orthotic support.

Four months after the first treatment a second treatment with BTX-A was given, aiming to reduce the severe hypertonia of the calf muscles of the right leg. The following therapeutic scheme was used, with the same dilution as before: gastrocnemius muscle: 140 units and soleus muscle: 60 units. Within one week after BTX-A treatment the muscle tone of the right lower leg decreased substantially and a corrective orthosis for the ankle joint could be fitted. Almost simultaneously with the reduction of the muscle tone in the leg the patient again complained about constipation. He also reported tiredness and difficulty with swallowing. Treatment with laxatives was started again. After one month the constipation wore off and the medication could be withdrawn. This time the reduction of muscle tone lasted for six weeks after BTX-A therapy.

Electromyography of distant muscles of the upper limbs could not be performed due to the severe spasticity.

In view of the generalized character of the spasticity it was decided to treat this patient with intrathecal Baclofen (ITB). After a successful therapeutic trial one year ago a Synchromed® infusion system was implanted. At the time of this report the spasticity remains under control (MAS 1) and so far no systemic complaints have been reported.

Case 3

A 19-year-old woman sustained severe brain injury after a ten meters fall. The Glasgow Coma Score at admission to the Intensive Care Unit was 6. Magnetic resonance imaging of the brain showed diffuse contusional lesions and oedema. Furthermore, she presented a lesion of the third cranial nerve and multiple fractures of the pelvis, left clavicle, acromion, and several ribs. A splenectomy had to be performed due to a spleen rupture. The hospital stay was complicated by a pulmonary embolism and a deep venous thrombosis. She also developed heterotopic ossification at the left hip and the right knee. Half a year later, the patient was referred to the rehabilitation centre for further treatment. At admission the patient presented a hypertonic tetraplegia, with limited range of motion of the left elbow and both knees. She was not able to stand without support and was unable to walk even with walking aids or manual assistance. She was otherwise incontinent for urine and completely dependent for all daily activities, including eating and personal hygiene.

The MAS was 2 for the right arm, and 1 for the left arm and both legs. However, the spasticity of the left arm increased during the following months to a MAS 3, but patient's mother refused pharmacological treatment either with systemic spasmolytic medication or local neuromuscular blocks. Intensive physical therapy and orthotic management for the elbow and knee contractures re-

sulted in a slight improvement of the range of motion of the right arm and the knees. Nevertheless, the muscle tone of the left arm increased further, causing painful spasms of the arm. Eventually, one year after trauma, patient's mother gave her consent for treatment of the left arm with BTX-A injections. Dysport® (Ipsen) was used in a volume of 2.5 ml per vial of 500 units. The left biceps muscle was injected at two sites with 150 units of Dysport® each and the brachioradial muscle with 200 units; 500 units in total.

The patient was evaluated two weeks after the injections. A remarkable reduction of the spasticity of the left arm flexors was seen (MAS 1). She was able to dissociate flexor and extensor movements selectively. However, the mother reported that three days after BTX-A treatment her daughter was hindered by severe constipation and was feeling more tired than usual. She also noticed that speech articulation and swallowing had become more difficult. At first, the constipation responded positively to treatment with Bisacodyl. However, the patient decided on her own to withdraw the medication and the constipation appeared again. After resuming the Bisacodyl one week later, the constipation wore off. These symptoms persisted during three months. The therapeutic effect on the left arm lasted for five months after the initial BTX-A treatment. Because of the aforementioned complication, the patient and her mother refused a second injection. At the last control visit, two years after trauma, the range of motion of the left arm was maintained with orthotic support and the elbow flexors showed a MAS of 2. She reported no gastrointestinal nor swallowing complaints.

DISCUSSION

Although the therapeutic goals were reached in all three patients, they repeatedly showed severe constipation as an autonomic side-effect after treatment sessions with BTX-A injections. As the colon is not in close proximity to the injection sites, this symptom is likely related to a systemic effect of BTX-A. We have performed this treatment in over 50 children and over 200 adults. After each intervention, a list with all possible side-effects had to be filled out by the patient or by the caregiver. All these data were entered into a database. Although in 10 patients side-effects occurred, only in these three patients constipation was reported during evaluation.

The action of BTX-A appears to be limited to cholinergic terminals where BTX-A inhibits release of acetylcholine and co-transmitters in both somatic and cholinergic autonomic terminals.^{8, 9} In the first patient described a slow repetitive stimulation of a motor nerve (RNS) was performed in order to investigate the presumed systemic reaction on BTX-A (figure 7.1). Electromyographic recordings were made from the hypothenar while stimulating the ulnar nerve at the wrist. The amplitude of the initial response was normal, but after prolonged 3 Hz stimulation a slight decremencing response occurred. An average of 11%

decrement in amplitude was visible from sixth to eighth compound muscle action potentials. This indicates that fewer muscle fibers responded to nerve stimulation during a train of stimuli, due to generalized blockage of acetylcholine release in nerve terminals. The patient did not show generalized weakness.

Figure 7.1 In the first patient described a slow repetitive stimulation of a motor nerve (RNS) was performed in order to investigate the presumed systemic reaction on BTX-A. EMG recordings were made from the hypothenar while stimulating the ulnar nerve at the wrist. The amplitude of the initial response was normal, but after prolonged 3 Hz stimulation a slight decrementing response occurred. An average of 11% decrement in amplitude was visible from sixth to eighth compound muscle action potentials. This indicates that fewer muscle fibers responded to nerve stimulation during a train of stimuli, due to generalized blockage of acetylcholine release in nerve terminals. The patient did not show generalized weakness.

The efficacy of BTX-A in children with adductor spasticity was demonstrated in a randomized controlled trial by Mall et al. using the Goal Attainment Scale.³ The safety profile of BTX-A (Dysport®) in patients with muscle hypertonia was ret-

respectively studied by Bakheit et al. and they reported adverse events in only 7% of treatment.¹³ Incidence of adverse effects was related to the total dose rather than the dose calculated on basis of body weight. The highest incidence of adverse events was observed in patients who received more than 1000 IU of BTX-A per treatment session. Constipation as a remote autonomic side-effect was not reported in this publication.

Autonomic function as a measure of side-effects using Dysport® in a range of doses (18–44IU/kg) was studied by Robertshaw et al.¹⁴ Their hypothesis was that BTX-A might reduce parasympathetic activity and, therefore, cardiac variability. They conclude that BTX-A is safe using the standard dosage. Only 1 out of 30 children had distant side-effects, which lasted for 6 weeks. Constipation was not mentioned as a side-effect.

Autonomic side-effects occur far more often after Botulinum Toxin-B (BTX-B).¹⁵ In a group of 30 patients (24 cervical dystonia; 6 hyperhidrosis) constipation was observed as a remote side-effect in 3 patients.

In a double blind randomized trial, autonomic function after BTX-A or B was studied in patients with cervical dystonia.¹⁶ More patients treated with BTX-B showed constipation as compared to those treated with BTX-A (3/9 vs 0/11).

In a retrospective study, constipation as a side-effect of BTX-A (Botox®) treatment on upper limb impairment and function was observed in 1 of 18 patients (aged 2–17 years).¹⁷ Furthermore, severe dysphagia has been reported as a remote side-effect of BTX-B treatment of the lower limbs and lumbar paraspinal muscles in a 29-year-old woman.¹⁸

Our patients repeatedly showed constipation as an adverse remote effect in response to BTX-A interventions. An explanation for this individual sensitivity is difficult. Probably it is in line with the observed interpersonal variability in autonomic ratio (AR) as described by Robertshaw et al. studying the effects of BTX-A on ECG parameters.¹⁴ This study reported that the child suffering from distal side-effects for 6 weeks, had the lowest AR.

Dysfunction observed in the gastro-intestinal tract is not uncommon in neurologically handicapped patients. The enteric nervous system contains more neurons than the spinal cord.¹⁹ Therefore, it is not surprising that generalized insults to the central nervous system (i.e. asphyxia or ischemia) may result in significant neural dysfunction in the gastro-intestinal tract as is shown for the spinal cord.²⁰ On the other hand, feeding and intake problems may result from various (motor) problems other than the increased muscle tone observed in these patients. However, from a clinical point of view there is a strong indication that the gastro-intestinal problems in these 3 patients appeared in connection with the BTX-A treatment.

CONCLUSION

We conclude that severe constipation may be an autonomic systemic side-effect of BTX-A treatment due to blockade of autonomic neurons via systemic spread. Knowledge of this possible side-effect is important for those who treat patients already at risk for gastro-intestinal dysfunction. A carefully taken clinical history during the treatment period makes prevention and management possible. Because the adverse effects were treatable and transitory, we believe that constipation per se is not an absolute contra-indication if, from a therapeutic view point of view, BTX-A treatment is indicated.

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CHAPTER VIII

LONG-TERM FOLLOW-UP ON INTRATHECAL BACLOFEN THERAPY IN NON-AMBULANT CHILDREN WITH INTRACTABLE SPASTIC CEREBRAL PALSY

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In preparation

ABSTRACT

Background

A couple of years ago, Hoving et al performed methodologically well-designed studies on ITB therapy in 17 children with intractable spastic CP. Follow-up showed positive effects on pain, ease of care, and mental health to be present 1 year after pump implantation.

Long-term results of ITB therapy in children with intractable spastic CP are limited, especially with regard to outcomes relevant to the patient and his / her caregivers.

Aims

The aims of this long-term follow-up study were threefold: I: to determine whether or not beneficial effects of ITB therapy are still present 6–9 years after commencement of treatment in the 17 children initially described by Hoving et al, II: to describe the course of these effects over time, and III: to investigate whether or not caregivers would still choose ITB therapy for their child considering the advantages and disadvantages they have experienced.

Methods

The parents of the 17 children filled out the Child Health Questionnaire (CHQ), current satisfaction on a Visual Analogue Scale regarding previous set treatment goals, a questionnaire concerning functioning of their child, and a self-made questionnaire.

Results

One parent did not return the CHQ questionnaire. Previous identified beneficial effects were found to still be present 6–9 years after commencement of treatment. Minimal improvement can still be expected 12 months after pump-implantation, especially for individually defined treatment goals and physical QoL. Ninety-four percent of the care-givers would choose for ITB treatment again.

Conclusion

This study shows that beneficial effects after ITB are still present 6–9 years after commencement of treatment in non-ambulant children. Minimal improvement can still be expected 12 months after pump-implantation, especially for individually defined treatment goals. Ninety-four percent of the care-givers would choose for ITB treatment again.

INTRODUCTION

Intrathecal baclofen (ITB) therapy is the direct administration of Baclofen into the intrathecal space by means of a neurosurgically placed catheter. The catheter is attached to a pump which is implanted subcutaneously or subfacially in the abdomen. This invasive treatment modality has been proven effective for the treatment of intractable spasticity in non-ambulant children with cerebral palsy (CP).¹⁻⁴ ITB therapy has the large advantage of by-passing the blood-brain-barrier (BBB). Orally administered Baclofen passes the BBB poorly and therefore results in high blood levels (hence side-effects) and almost undetectable cerebrospinal fluid levels of Baclofen (hence low therapeutic effect). When administering Baclofen intrathecally a hundredth part of the oral dose of Baclofen is sufficient to effectively reduce spasticity.⁵ Therefore the side-effects encountered when Baclofen is administered orally can be prevented.

Between 2006 and 2009, Hoving et al published the results of a Dutch national study in seven articles addressing safety, efficacy, and cost-effectiveness of ITB therapy in a group of 17 carefully selected children with intractable spastic CP. At that time there was a lack of methodologically well-designed studies in this field. Therefore, they used a double blind, randomised, placebo-controlled design for the ITB dose-finding test treatment study and a prospective, randomised design for the open-label pump implantation study. In this Dutch national study, continuous infusion of ITB (CITB) relieved pain, facilitated ease of care, and improved mental health. The majority of children could extend their activities and participation. During a mean follow-up of 18.4 months (12–24), Hoving et al recorded 80 adverse events. Eight adverse events were serious, but none were life-threatening and none of the children needed to be hospitalised. During the last follow-up visit, 15 of the 17 children and/or their parents stated that they were satisfied with CITB and would participate in all ITB related procedures again. Two parents were not sure they would have the pump implanted in their child again, in spite of the achieved individual treatment goals.

Since then several interesting articles and commentaries have been published. Recently, Morton et al found ITB therapy to improve quality of life (QoL; comfort, ease of care) and to reduce muscle tone and spasms in 38 non-ambulant children aged 5–16 years with spastic CP over a sustained period of 18 months after pump implantation.⁶ Minimal effects on function, participation in society, and contracture formation were found.⁶

In a reply to this study Miller made two important remarks.⁷ Firstly, he stated that expecting to observe a functional gain after ITB therapy in non-ambulant children with CP is unrealistic. Most of the times the goal is to improve comfort and facilitate care-giving, which can be reported by care-givers. Secondly, he criticized the short term follow-up on a treatment that is probably going to be continued for 50–60 years.

Another recently published study is the one by Motta et al in which it was stated that ITB improves Gross Motor Function Measurement scores, Ashworth scale scores, Barry-Albright dystonia scores, and functional ability in 37 patients (18 males, 19 females; GMFCS level 2: n=9; level 3: n=13; level 4: n=7; level 5: n=8).⁸

In a reply to this study Krach highlighted some methodological limitations of the study by Motta et al, but also stated that these limitations might be inevitable in children with neurodisability.⁹ She suggested the single-participant experimental design that uses the individual as his / her own comparison as an option for future research. This merits the establishment of sufficient baseline measurements.

Acting upon these remarks made by Miller and Krach we prolonged the well-designed study by Hoving et al 6–9 years after pump implantation.^{3, 4, 10} Our aim was to study: I: whether or not beneficial effects of ITB therapy are still present 6–9 years after commencement of treatment, II: the course of effects after ITB treatment over time, and III: whether or not caregivers would still choose this treatment modality for their child again considering the advantages and disadvantages of ITB therapy now known.

METHODS

Design

This prospective follow-up study is a continuation of the prospective Dutch national study on the efficacy and safety of CITB in 17 children with intractable spastic CP (figure 1).^{3, 4, 10} Their parents were informed about the study and all agreed to participate.

Figure 8.1 Follow-up diagram of the 17 children with intractable spastic CP treated with CITB therapy

This follow-up study was approved by the Medical Ethics Committee of the Maastricht University Medical Centre (MUMC) according to Dutch governmental guidelines.

Participants

The 17 children with bilateral CP consisted of 9 girls and 8 boys with a mean age of 21.1 years (SD 3.1; 14–25). One boy was GMFCS level 3; 1 boy and 1 girl were

both GMFCS level 4; 14 children were GMFCS level 5. Mean follow-up on pump implantation was 7.5 years (SD 0.9; 6–9).

Outcome measures

After all these years we were mainly interested in the QoL and the satisfaction for the initially defined treatment goals of these children. The child health questionnaire (CHQ) and the visual analogue scale (VAS) were chosen as outcome measures as these instruments have shown to be capable of detecting improvements.^{3, 4, 10}

The CHQ is a generic QoL instrument which measures 14 unique physical and psychosocial concepts.¹¹ In this present study the 50-item, parent-form was used (CHQ-PF50). All domains are scored on a 0–100 scale with higher scores reflecting better QoL. Physical and psychosocial summary scores can be derived from the separate CHQ profile scores which have a mean of 50 and an SD of 10 in the general population.

To measure satisfaction the VAS was used. This is a straight 10-cm horizontal line with the anchor points “very satisfied” (score 10) and “very dissatisfied” (score 0). This is opposite to how the VAS is commonly used, but in line with the previous studies by Hoving et al. Although, the parents were reminded of the three treatment goals defined before pump-implantation, they were not informed about the previous scores. They scored their current satisfaction with regard to these goals on the VAS. The mean of these 3 VAS scores was used for statistical analysis (individual VAS). VAS scores for improvement of ease of care and relief of pain were analyzed separately as these were the most frequently formulated treatment goals.

Additionally, we wanted to know whether or not caregivers would still choose ITB therapy for their child at present considering the advantages and disadvantages encountered over the last 6–9 years. As caregivers might not be aware of changes detected by the CHQ questionnaire and the VAS, we used a questionnaire which addresses improvement / worsening of functioning of their child by means of 40 questions. Questions are scored on a 5-point Likert scale (“A lot worse” – “Slightly better” – “The same” – “Slightly better” – “A lot better”). This questionnaire was developed by Staal et al who used it to identify areas of positive improvement after ITB therapy in 49 individuals.¹² It has also been used by Krach et al in order to evaluate satisfaction regarding ITB therapy in 100 patients / caregivers.¹³ This questionnaire was carefully translated into Dutch.

Furthermore, parents answered questions with regard to pain caused by the ITB pump, side-effects at present time, hospitalizations, and surgeries since ITB pump implantation, and finally whether or not they would choose ITB therapy for their child again.

Statistical analysis

PASW statistics 18 was used for statistical analysis. The non-parametric Wilcoxon Signed Rank Test was used to compare present CHQ and VAS scores to baseline and 1 year post-implantation CHQ and VAS scores.

RESULTS

The caregivers of all 17 children participated in the study. Only one caregiver did not return the CHQ questionnaire due to an ongoing divorce. All other data were available.

Beneficial effects of ITB therapy 6–9 years after commencement of treatment

In table 1 the means and standard deviations of CHQ and VAS scores of the 17 children at 4 different moments in time can be found: before pump implantation (baseline), at 6 months post-implantation, at 12 months post-implantation, and at present (6–9 years after pump-implantation). Furthermore, present CHQ and VAS were compared to scores at baseline and scores at 12 months post-implantation. It can be seen that there are no statistically significant differences between present scores and scores at 12 months post-implantation. The positive effects on pain, ease of care, and mental health are still present. Moreover, additional benefits have appeared i.e. significantly improved scores on the Parent Impact – Emotional subscale, Parent Impact – Time subscale, and the Physical Summary.

Table 8.1 VAS and CHQ at baseline and up to 9 years after CITB therapy in 17 children with intractable spastic CP

Variable	Baseline		6 months		12 months		6 – 9 years			p [#]	
	n	Mean (SD)	Mean (SD)	p [*]	n	Mean (SD)	p [*]	n	Mean (SD)		
VAS											
Individual problems	17	2.2 (1.1)	6.3 (1.7)	0.00	17	6.9 (1.8)	0.00	17	6.90 (1.51)	0.000	0.796
Care	16	2.0 (1.0)	6.4 (1.9)	0.00	16	7.1 (2.0)	0.00	16	7.26 (2.15)	0.000	0.959
Pain	12	2.4 (1.9)	7.0 (2.0)	0.00	12	7.8 (1.9)	0.00	12	8.01 (1.29)	0.002	0.790
CHQ											
Physical functioning	17	2.8 (5.4)	3.3 (7.4)	0.67	17	4.9 (12.4)	0.89	16	10.06 (25.52)	0.463	0.715
Role-Emotional/Behavioral	16	58.4 (43.1)	72.2 (37.7)	0.26	16	75.8 (31.5)	0.12	15	53.20 (45.07)	0.799	0.153
Role-Physical	16	49.9 (42.2)	57.3 (37.0)	0.48	16	57.3 (35.6)	0.44	14	48.64 (42.55)	0.916	0.592
Bodily pain/discomfort	17	46.8 (27.8)	71.2 (25.5)	0.00	17	72.4 (20.8)	0.02	16	74.38 (15.48)	0.002	0.599
General behaviour (BE)	16	77.1 (9.0)	83.3 (10.9)	0.02	16	78.4 (11.3)	0.62	15	84.62 (10.28)	0.074	0.116
Mental health	17	67.2 (11.3)	77.5 (12.2)	0.00	17	77.1 (11.0)	0.01	16	75.94 (12.68)	0.010	0.634
Self-esteem	16	65.3 (13.6)	68.4 (16.2)	0.51	16	68.4 (16.3)	0.84	16	72.74 (10.94)	0.073	0.306
General health	17	55.8 (21.2)	54.2 (17.4)	0.80	17	54.0 (19.8)	0.67	16	62.91 (20.58)	0.224	0.049
Parental impact-Emotional	16	66.0 (28.6)	74.9 (22.1)	0.55	16	71.4 (19.2)	0.21	16	78.23 (16.50)	0.008	0.223
Parental impact-Time	16	68.9 (25.9)	84.1 (25.1)	0.08	16	83.4 (21.4)	0.13	16	91.75 (14.76)	0.002	0.105
Physical Summary	16	17.6 (10.5)	21.4 (9.5)	0.13	16	22.1 (9.5)	0.16	13	27.40 (11.83)	0.019	0.196
Psychosocial summary	16	48.8 (8.7)	55.0 (9.9)	0.02	16	54.2 (7.0)	0.09	13	53.98 (5.67)	0.087	0.972

* Compared to baseline # Compared to 12 months post-implantation

The course of effects of ITB therapy over time

Figure 2 shows the course of 4 outcome measures over time: the physical (PhS) and psychosocial summary scores (PsS) of the CHQ questionnaire, and the VAS scores for improvement of pain and ease of care. It is evident that treatment effects are still present 6–9 years after commencement of treatment. Although it seems that the effect stabilizes, minimal improvement can still be expected 12 months after pump-implantation, especially for individually defined treatment goals. Furthermore, it appears that improvements in terms of physical QoL (CHQ PhS) need more time to become evident. At 12 months post-implantation there was no statistically significant difference compared to baseline ($p = 0.16$); however, at 6–9 years post-implantation there is ($p = 0.02$).

Figure 8.2 Box and whisker plots of 2 VAS scores (pain and ease of care) and 2 CHQ summary scores (PhS and PsS)

Caregivers choosing ITB therapy for their child again

The advantages as measured by means of the CHQ and the VAS have already been described (figure 2). In addition, parents rated improvement / worsening for 40 domains of functioning on a 5-point Likert scale (figure 3). It can be seen that improvements were more frequent than worsening for all questions, except

for questions 6 (drooling) and 19 (bladder control). Improvements were most frequently noted for questions 1 (ability to transfer), 27 (startle movements, sudden jerks), and 29 (sleeping at night).

Figure 8.3 Caregivers responses to 40 questions with regard to improvement / worsening of functioning after 6–9 years of CITB treatment

The disadvantages were measured in terms of pain caused by the pump, device related problems, number of hospitalizations, number of surgeries, and side-effects at present time. Two out of seventeen children were reported to experience pain caused by the pump. During these 6–9 years of follow-up 11 device-related problems were encountered: 2 pump-related problem (failure of the pump; subsidence of the pump), 6 drain-related problems (drain too high: 2; drain too low: 1; drain too superficial: 1; drain obstructed: 2), and 3 refill-related problems. Every child was hospitalized at least once since pump-implantation (28 hospitalizations in total; range 1–4). Most of these were ITB-related (18/28), but mainly involved substitution of the pump (15/18). Three out of 17 children underwent orthopedic surgery (all scoliosis). Forty-three side-effects at present were reported for 17 children.

If given the choice, sixteen parents (94%) would choose ITB therapy for their child again, and 1 parent was not sure.

DISCUSSION

Previous studies have addressed the long-term effects of ITB therapy in children with CP. However, most of them were retrospective, had a broad range of follow-up months, did not include QoL and other subjective outcome measures, did not perform sufficient baseline measurements, included both ambulant and non-ambulant children, had large numbers of drop-outs, and / or included (adult) patients with spasticity not due to CP.^{14–19} In our opinion, the present study is unique because of the systematical evaluation of the 17 ITB treated children over a long period of time. At baseline and at 3, 6, 9, and 12 months after pump-implantation a comprehensive set of outcome measures was used and the outcome measures showing benefits were also used in this present study 6–9 years after pump implantation.

It was shown that the previous identified positive effects on pain, ease of care, and mental health are still present 6–9 years post-implantation. Moreover, additional benefits have appeared, e.g. significantly improved scores on the Parent Impact – Emotional subscale, and the Parent Impact – Time subscale. According to the CHQ manual this means that care-givers experience fewer feelings of emotional worry / concern and fewer limitations in time available for personal needs due to the child's physical and / or psychosocial health.¹¹ It is difficult to tell whether this is a direct result of ITB therapy or whether this would also occur in parents of children with CP not receiving ITB therapy. An ever growing amount of experience in caring for their children could explain the decrease in worries and concern and the increase in time for personal needs of the care-givers.

Another additional benefit was present 6–9 years after pump implantation, i.e. significantly improved scores on CHQ PhS. The subscales that contribute most profoundly to the PhS are physical functioning, role/social limitations (physical), bodily pain/discomfort, and general health.¹¹ It appears that improvements in CHQ PhS need more than 12 months to become evident (figure 2). A possible explanation for this observation is that improvements in terms of CHQ PhS require more than a reduction in spasticity alone. New possibilities have to be explored and practiced, which takes some time. On the other hand, a reduction in spasticity will cause an immediate effect on pain and ease of care (figure 2).

Although it seems that the improvements reach somewhat of a plateau 12 months after pump-implantation, minimal improvement can still be expected at that time, especially for individually defined treatment goals. This is important information for children and care-givers (who consider ITB therapy).

Regardless of the side-effects, the complications, and the necessity of eventually substituting the pump, 94% of the care-givers would choose ITB therapy for their child again. This is a common finding in literature, highlighting the high satisfaction with ITB therapy.^{2, 13, 20–22}

Although this study is one of the first with such an extensive follow-up on ITB therapy in children with intractable spastic CP, this is only the beginning. Large groups of children receiving ITB therapy should be measured by means of multiple outcome measures at baseline and systematically up until 50–60 years after pump implantation. Using both objective and subjective outcome measures in both quantitative and qualitative designed studies are needed to determine the very long-term effects of ITB therapy.

Limitations

This study has several limitations.

Firstly, the questionnaires were filled out by the care-givers and not the patients themselves. However, in this present study self-reports would have been extremely difficult to obtain and interpret given the severity of disability of the majority of the children with CP. In this case, parents / caregivers are the most logical source of information as they are assumed to have intimate knowledge of the child.

Secondly, the questionnaire developed by Staal et al has not been validated.¹² The development of a well-constructed, validated, and easy to administer long-term outcome measure specific for ITB treatment would be highly useful. This should include both beneficial effects of ITB therapy on all domains of the ICF and detrimental effects in terms of side-effects, complications, hospitalizations, and surgeries.

Finally, we did not search for correlations with other factors that might influence outcome such as major life events, additional treatments, and aging.

CONCLUSION

This study shows that beneficial effects after ITB are still present 6–9 years after commencement of treatment in non-ambulant children. Minimal improvement can still be expected 12 months after pump-implantation, especially for individually defined treatment goals. Ninety-four percent of the care-givers would choose for ITB treatment again. This information is very useful for physicians and can be used to inform patients and their care-givers who are considering ITB therapy. Future studies should aim at measuring large groups of children receiving ITB therapy by means of multiple outcome measures at baseline and systematically up until 50–60 years after pump implantation.

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CHAPTER IX

QUALITY OF LIFE OF CHILDREN WITH CEREBRAL PALSY:

A cross-sectional KIDSCREEN study in the Southern part of the Netherlands

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Submitted

ABSTRACT

Objective

To compare the quality of life (QoL) of 8–18 year old children with cerebral palsy (CP) in the Southern part of the Netherlands to a sample of European children from the general population and to investigate factors associated with possible differences.

Design

A cross-sectional KIDSCREEN-52 (by-proxy version) study.

Subjects / patients

The parents of 80 out of 81 children (mean age 13.4 years, SD 2.98; 49 boys, 31 girls; Gross Motor Function Classification System (GMFCS) level 1: 21, 2: 5, 3: 16, 4: 18, 5: 20) agreed to participate.

Methods

Two-sample T-tests were used to compare domain scores between groups. Regression analysis was used to identify factors associated with deviant QoL scores.

Results

Significantly higher QoL compared to the reference population was reported for the parent relation & home life and school environment domains. Significantly lower QoL was reported for the physical well-being, social support & peers, and social acceptance domains. Lower cognitive levels, less communication skills, and higher GMFCS levels were associated with some of the above mentioned domains of QoL.

Conclusion

This study exposed and provided possible explanations for problem domains of QoL in children with CP living in the Southern part of the Netherlands. This information can be used to inform caregivers and service-providers.

INTRODUCTION

In recent years there has been increasing interest in the Quality of Life (QoL) of children with Cerebral Palsy (CP) (figure 9.1: pubmed search; MeSH terms: “Quality of life” AND “Cerebral Palsy”). The World Health Organization (WHO) defines QoL as “an individual’s perception of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns”.¹ Technically speaking QoL is not a definition; it is a concept, an invention of the human mind to construct a model of the world.² As with all human inventions, it is not perfect and therefore QoL does not represent one single truth. Nevertheless, attempts should be made to capture and analyse this QoL in the best way possible as it may expose problem areas in chronically ill children and could lead to treatment opportunities.

Figure 9.1 Number of publications on QoL of patients with CP (pubmed; MeSH terms: “Quality of life” AND “Cerebral Palsy”)

There are several instruments claiming to be able to assess QoL of children with CP, e.g. the Pediatric QoL Questionnaire CP Module (PedsQL), the Child Health Questionnaire (CHQ), the CP QoL questionnaire for children (CP QoL-Child), and the KIDSCREEN. As all these different QoL instruments make it more and more difficult for researchers and clinicians to interpret and compare data found, studies have been conducted to identify the most appropriate QoL questionnaire for their purpose.³⁻⁵ Although clearly the most commonly used instrument internationally⁵⁻⁷, the CHQ was outperformed conceptually and psychometrically by the KIDSCREEN in a study by Davis et al with 204 primary caregivers of children with CP.³ The KIDSCREEN is a modern, generic QoL instrument, which uses questions based on focus-groups with children and adolescents all over Europe.⁸⁻¹⁰ It focuses entirely on subjective perceptions, has shown to possess excellent psychometric properties, can be used for both disabled and non-

disabled children, and can be reported by both the children themselves and their caregivers.⁸⁻¹¹

Previous studies have assessed QoL of children with CP. Several smaller studies found contradicting results.^{6, 7, 12, 13} The largest study so far (Study of Participation of Children with CP Living in Europe (SPARCLE), 7 European countries, KIDSCREEN-52) found that QoL of children with CP aged 8–12 years is, on average, similar to that of children in the general population on practically all domains.¹⁴ This study provided clues that children with CP have a slightly better school environment, but experience lower autonomy. Specific factors were found to be associated with lower QoL in certain domains, e.g. pain is associated with less QoL in the physical and psychological well-being and self-perception domains.¹⁵ Greater limitations, on the other hand, led to higher or lower QoL depending on the domain. However, impairment and pain could only explain a small amount of variance in QoL, which is therefore likely to be largely determined by social and environmental factors.

Given that social and environmental factors can differ significantly between countries and even regions and since the Netherlands did not participate in the SPARCLE study, a study was performed to describe the QoL of the entire population of children with CP in the Southern part of the Netherlands by means of the by-proxy version of the KIDSCREEN-52. As a first step the QoL profile of these children will be displayed. Next, a comparison is made to the QoL of a European sample of children (including Dutch children) from the general population⁹ in order to determine problem domains in Dutch children with CP. Finally, factors associated with problem domains of QoL are investigated.

METHODS

Design

The parents of all 81 children with CP aged 8–18 years seen at the outpatient clinic of the Maastricht University Medical Centre (MUMC), were informed about the study and were asked whether they were willing to participate. All except one agreed to participate. After permission was obtained, parents were sent the by-proxy version of the KIDSCREEN-52 and a questionnaire concerning basic characteristics (table 9.1).

This cross-sectional study was approved by the Medical Ethics Committee (MEC) of the MUMC according to Dutch governmental guidelines.

Table 9.1 Characteristics of the children with CP living in the Southern part of the Netherlands

	Mean (range) Frequency (%)		Mean (range) Frequency (%)
N	80	Age (years)	13.4 (8–18)
Sex		Sensory disability	
M	49 (61%)	Visual	14 (18%)
F	31 (39%)	Auditory	2 (3%)
Type CP		Feeding	
Spastic unilateral	26 (33%)	I: Without difficulties	64 (80%)
Spastic bilateral	52 (65%)	II: Significant Difficulties	9 (11%)
Dyskinetic	1 (1%)	III: Stoma	6 (8%)
Ataxic	1 (1%)	Missing	1 (1%)
Cognitive level		Pain / discomfort	
< 50	22 (28%)	None	50 (63%)
50–70	22 (28%)	Some - severe	28 (35%)
>70	36 (45%)	Missing	2 (3%)
GMFCS		Communication Skills	
I	21 (26%)	I: Normal	47 (59%)
II	5 (6%)	II: Problems	17 (21%)
III	16 (20%)	III: Alternatives	7 (9%)
IV	18 (23%)	IV: None	8 (10%)
V	20 (25%)	Missing	1 (1%)
Wheelchair dependent		Level of hand functioning	
Yes	38 (48%)	I: No limitations	15 (19%)
No	42 (53%)	II: Limitations with fine motor task in both hands	22 (28%)
Family composition		III: Needs assistance in performing tasks	18 (23%)
Two parents family	73 (91%)	IV: Needs assistance and makes use of adaptive equipment	5 (6%)
One parent family	3 (4%)	V: Requires assistance in everything	18 (23%)
Missing	4 (5%)	Missing	2 (3%)
Epilepsy		Occupation parents	
None the last year	62 (78%)	≥1 parent works fulltime	53 (66%)
< 1 / month last year	13 (16%)	Other situation	24 (30%)
> 1 / month last year	5 (6%)	Missing	3 (4%)
Schooltype		Parental qualification	
Normal education	27 (34%)	None	4 (5%)
Special education	50 (63%)	Below university	67 (86%)
Missing	3 (4%)	University degree	7 (9%)
Living area		Missing	2 (3%)
Urban	40 (50%)		
Countryside	38 (48%)		
Missing	2 (3%)		

Participants

The 80 children with CP consisted of 49 boys and 31 girls with a mean age of 13.4 years (SD 2.98). Forty-eight per cent of the CP children were wheelchair dependent and 55% had cognitive levels below 70. The major patient and socio-demographic characteristics are displayed in table 9.1.

Outcome measures

The KIDSCREEN-52 is a generic QoL instrument for children aged 8–18 years and was validated psychometrically with 22110 European children from the general population all over Europe.^{9, 10} It consists of 52 items assessing QoL in ten domains (table 9.2). Items are scored on a 5-point Likert-scale (“never-seldom-sometimes-often-always” / “not at all-slightly-moderately-very-extremely”). Missing values are to be replaced by the mean of the other items belonging to the same domain if no more than 1 item is missing for that domain.

Table 9.2 Explanation of the KIDSCREEN domains^{9, 14}

Domain	Aspects measured
Physical Well-being	Physical activity, energy, and fitness
Psychological Well-being	Positive emotions and satisfaction with life
Moods & Emotions	Negative moods, boredom, and stress
Self-Perception	Self, bodily appearance, and body image
Autonomy	Freedom of choice and self-determination in leisure time
Parent Relation & Home Life	Interactions and relationships with parents and the socioemotional atmosphere at home
Financial Resources	Adequacy of pocket money relative to peers
Social Support & Peers	Social support available from friends and peers
School Environment	Learning and feelings about school and teachers
Social acceptance	Social acceptance or rejection by peers, including bullying

Two ways of calculating domain scores are used in literature. First, item responses can be summed for each domain and are then rescaled to a 0–100 scale (sum-scores), with higher scores indicating better QoL. These sum-scores are used when describing the QoL profile of a population.^{15, 16} Second, Rasch Person Parameters can be computed for each dimension, which are then transformed into T-scores with a mean of 50 and an SD of 10. Higher T-scores indicate higher QoL. T-scores are used when comparing QoL between populations.¹⁴

In this study, both sum-scores and T-scores will be used to describe the QoL profile of the population of children with CP living in the Southern part of the Netherlands. This will enable future studies to compare their results to Dutch children with CP.

T-scores will be used to compare the QoL of children with CP living in the Southern part of the Netherlands to a sample of European children (aged 8–18 years) from the general population. Unfortunately, as parent-reported T-scores are not available for the European population of children with CP, no comparison can be made to this group of children.¹⁵

Statistical analysis

After all the parents returned the questionnaires all data were entered into SPSS 18.0 for statistical analysis (RH). Afterwards, data entry was randomly checked and found correct by another researcher (JH).

The SPSS syntax provided by the KIDSCREEN group Europe was used to calculate Rasch Person Parameters and T-scores for each of the ten domains.¹⁷ Furthermore, item responses were summed and rescaled to a 0–100 score (sum-scores). Floor and ceiling effects were considered to be present if the proportions of respondents with the maximal resp. minimal scores for each domain were > 15%.¹⁸ Stata/ES 9.0 was used to perform two-sample T tests in order to compare the T-scores of the children with CP living in the Southern part of the Netherlands to the general population of European children.^{9, 15} Given the number of hypotheses tested, an alpha of 0.01 was considered significant.

Regression models were used to investigate the association between patient and sociodemographic characteristics and T-scores of domains in which children with CP living in the Southern part of the Netherlands score significantly different compared to the sample of European children from the general population. Linear regression analysis was used which meant that logistic transformation of the social acceptance and parent relation & home life domains had to be performed, as scores in these domains were not distributed normally. All factors identified using univariate (SPSS 18.0, dummy variables, $p < 0.1$) model testing were used for the subsequent multivariate model testing.

RESULTS

QoL profile of Dutch children with CP

In figure 9.2 box and whisker plots of the sum-scores of the 10 KIDSCREEN-52 domains of the 80 children with CP living in the Southern part of the Netherlands can be found. It is clear that the studied population scores relatively low in the physical well-being and social support & peers domains compared to the other domains of QoL. In table 9.3 the exact sum-scores (mean, SD, median, interquartile range, floor and ceiling effect) can be found. For the parent relation & home life, financial resources, and social acceptance domains ceiling effects were observed. No floor effects were observed.

Figure 9.2 Box and whisker plots of the KIDSCREEN sum-scores for 80 children with CP living in the South of the Netherlands

Table 9.3 Sum-scores of 80 children with CP living in the Southern part of the Netherlands

Domains	No. of items	CP - Southern part of the Netherlands					
		Sum-scores					
		Mean	SD	Median	IQR	Floor effect %	Ceiling effect %
Physical Well-being	5	58.0	21.5	55.6	38.9 – 77.8	0.0	2.5
Psychological Well-being	6	77.5	14.9	75.0	66.8 – 87.5	0.0	10.0
Moods & Emotions	7	78.8	16.1	82.1	67.9 – 92.9	0.0	6.3
Self-Perception	5	78.0	15.1	80.0	68.8 – 90.0	0.0	10.0
Autonomy	5	72.1	15.3	75.0	60.0 – 80.0	0.0	6.3
Parent Relation & Home Life	6	84.3	13.9	87.5	75.0 – 95.8	1.3	18.8
Financial Resources	3	73.2	26.0	75.0	58.3 – 100.0	3.8	23.8
Social Support & Peers	6	49.2	27.6	54.2	25.0 – 75.0	5.0	2.5
School Environment	6	80.3	17.9	83.3	70.8 – 95.8	1.3	8.8
Social acceptance	3	83.3	19.0	91.7	75.0 – 100.0	1.3	35.0

Comparison to a sample of European children from the general population

T-scores (mean, SD, comparison to a sample of European children from the general population) can be found in table 9.4. Again, low scores for the physical well-being and social support & peers domains are reported. Also, the children are reported to have low QoL in the social acceptance domain compared to the sample of European children from the general population. In contrast, significantly higher QoL is reported for parent relation and home life and the school environment domains.

Table 9.4 T-scores of 80 children with CP living in the Southern part of the Netherlands compared to a sample of European children from the general population

Domains	No. of items	N	Mean	SD	p*
Physical well-being	5	74/80	41.1	9.7	0.00
Psychological well-being	6	77/80	51.7	10.3	0.13
Moods & emotions	7	76/80	48.7	11.5	0.27
Self-perception	5	74/80	50.7	9.9	0.57
Autonomy	5	71/80	48.0	8.4	0.09
Parent relation & home Life	6	74/80	54.8	10.3	0.00
Financial resources	3	60/80	52.7	10.9	0.04
Social support & peers	6	65/80	40.0	15.4	0.00
School environment	6	71/80	56.4	11.1	0.00
Social acceptance	3	78/80	46.9	11.7	0.01

* Significance compared to the general population of European children (N = 15485 – 15897; Mean $\approx$ 50.00; SD $\approx$ 10.00, depending on the domain)⁹

Factors associated with domains of significantly different QoL in Dutch children with CP

Patient characteristics and sociodemographic factors (table 9.1) were investigated to see whether they were significantly associated with the physical well-being, parent relation & home life, social support & peer relations, school environment, and social acceptance domains (table 9.5). For the physical well-being domain it was found that higher GMFCS level was associated with lower T-scores. Less communication skills and lower cognitive levels were associated with lower T-scores in the social support & peers and school environment domains. Furthermore, parents with no educational qualification rated their child's QoL in the parent relation & home life domain higher. For the social acceptance domain no associated factors could be identified.

CHAPTER IX

Table 9.5 Factors associated with low QoL domains (T-scores) in Dutch children with CP (multi-variate analysis)

Domain	Independent variable	B	p
Physical well-being	GMFCS		
	Level 1	0.0	NA
	Level 2	-11.5	0.00
	Level 3	-10.6	0.00
	Level 4	-14.8	0.00
	Level 5	-16.5	0.00
Parent relation & home life	Parental qualification		
	No qualification	0.0	NA
	Below university	-1.1	0.00
	University degree	-1.0	0.00
Social support & peers	Communication skills		
	I: normal	0.0	NA
	II: Problems	-10.5	0.04
	III: Alternatives	-2.6	0.71
	IV: none	-15.7	0.02
	Cognitive level		
	> 70	0.0	NA
	50–70	-1.0	0.82
	< 50	-13.5	0.01
School environment	Communication skills		
	I: normal	0.0	NA
	II: Problems	3.6	0.06
	III: Alternatives	4.7	0.01
	IV: none	5.3	0.00
	Cognitive level		
	> 70	0.0	NA
	50–70	3.1	0.04
	< 50	3.7	0.00
Social acceptance	No factor identified		

NA = not applicable

DISCUSSION

To the best of our knowledge this is the first study to investigate QoL of Dutch children with CP by means of the KIDSCREEN-52. The main strength of this study is that 99% of the parents of all children with CP seen at the outpatient clinic of the MUMC participated. The overall QoL profile of children with CP living in the Southern part of the Netherlands seems to be quite similar to the

QoL profile of children with CP as found in the SPARCLE study.^{14, 15} For example, relatively high scores on the school environment domain and relatively low scores on the autonomy domain were found, which is in accordance with the study by Dickinson et al.¹⁴ These findings confirm the usefulness of the KIDSCREEN-52 across national borders. In this present study it was found that children with CP living in the Southern part of the Netherlands are reported to have low QoL on three KIDSCREEN-52 domains compared to a sample of European children from the general population, i.e. the physical well-being, social support & peers, and social acceptance domains.

Less physical well-being

According to the KIDSCREEN group Europe low scores in the physical well-being domain mean that more children than usual feel physically exhausted, unwell, and unfit.⁹ In this present study it was found that higher GMFCS levels were associated with lower QoL in this domain. This is a logical finding and is in accordance with the studies by Dickinson et al and Arnaud et al.^{14, 15} However, both Arnaud et al and Dickinson et al found pain to be associated with lower QoL scores. This was not the case in the present study. This discrepancy between our findings and literature may be due to the fact that dichotomous pain data were used. Furthermore, it could be that the relationship between QoL and pain is not as obvious as we expect it to be. For example, in a study by Engel et al it was shown that in adults with CP it is not the pain itself that influences psychological functioning, but the coping strategies in reaction to the pain.¹⁹

More family, less friends?

It is intriguing to see that these Dutch children with CP are reported to have significantly higher QoL in the school environment and parent relation & home life domains and significantly lower QoL in the social support & peers and social acceptance domains compared to a sample of European children from the general population. This is a pattern not observed in the European population of children with CP. We came up with two possible, non-exclusive explanations: one based on quantitative research, the other on qualitative research.

With regard to the first, in a large, cross-sectional survey study using the KIDSCREEN-52 among 16.210 children in children and adolescents 8–18 years old in 11 European countries, Analitis et al found that living in the Netherlands holds the highest odds ratio (1.68) of being bullied.²⁰ These results could explain why more Dutch children with CP than usual feel tormented, bullied, and rejected by peers. The observed pattern leads to the assumption that Dutch people committed to these children (parents, family, teachers, etc) have a significant positive contribution to their QoL, while non-committed others (peers) might bully and negatively influence their QoL.

The second explanation is based on qualitative research by Parkinson et al who investigated the extent of agreement between children with CP and their caregivers concerning their views on what contributed to the children QoL.²¹ They conducted qualitative interviews with 26 children with CP and 35 caregivers and came to the conclusion that there is considerable overlap but also some divergence. For example, children reported enjoying being on their own from time to time. Caregivers do not appreciate these attitudes and put substantial effort into creating opportunities for their child to be included socially. The interviewers found them very concerned about their child's experiences of being isolated or bullied by other children, often emphasizing this more than the children themselves. In other words, it is very well possible that low QoL on the social support & peers and social acceptance domains is due to concerns of the caregivers rather than what the children experience themselves. This is in accordance with our PARS-III study in which it was shown that children with CP psychosocially adjust to their motor and accompanying problems by withdrawal, without establishing sufficient and comprehensive peer relations. The question remains: who is right? Is it acceptable for children with CP to withdraw and enjoy time spent on their own, or are the caregivers right by stating that the children underestimate the risk and consequences of being socially isolated and that effort has to be put into engineering opportunities for their child to be included socially?

Comparison to the QoL of other patient populations in the Netherlands

Several other studies have investigated the QoL profile of specific patient populations in the Netherlands by means of the KIDSCREEN. For example, van Dijk et al found 65 child and adolescent retinoblastoma survivors to report good QoL compared to the reference population, with even significantly higher QoL for the moods & emotions and autonomy domains.²² Smets et al found no significant difference in QoL between 35 children with a positive carrier status for inherited cardiovascular diseases and the reference population.²³ The same was observed by Michielsen et al in 56 children and adolescents with congenital lower limb deficiency (LLD).²⁴ Therefore, we can state the QoL profile of Dutch children with CP to be unique as significant lower QoL was reported for three domains. As single physical (LLD) or psychological (fear of sudden cardiac death or recurrence of cancer) factors do not seem to influence QoL, one could argue that it is the interaction of multiple impairments met by Dutch children with CP which causes the decrease in QoL in certain domains.

Limitations of this study

An important limitation of this study is the sole reliance on proxy reports. The literature on the best source to evaluate QoL is inconsistent at best. The WHO

recommends that children should report their own QoL.²⁵ Furthermore, a recent study has shown that, especially in children with chronic neurological disorders, parent-children agreement is suboptimal and that parents under-report subjective aspects of well-being.²⁶ However Le Coq et al found 8 to 11 year old pediatric asthma patients to be less responsive and less reliable reporters on a QoL measure compared to their parents.²⁷ It is now becoming more and more accepted that there is no one single truth concerning QoL and therefore self-reports and proxy-reports are complementary.²⁸ With regard to the present study, self-reports would have been extremely difficult to obtain and interpret given the severity of disability of the majority of the population of the children with CP. This problem is omnipresent which is probably best illustrated by the SPARCLE study itself in which 318 out of the 818 selected children with CP could not self-report.¹⁴ In this case, proxy-reports are the only way to evaluate QoL with their parents / caregivers being the most logical source of information as they are assumed to have intimate knowledge of the child. This inevitably means that parents have to judge how their children experience life.

Furthermore, no data on parental stress was collected. Arnaud et al have shown that parents with higher levels of stress were more likely to report poor QoL on all domains.¹⁵

Finally, it was not possible to compare parent-reported T-scores of Dutch children with CP to parent-reported T-scores of an European sample of children with CP as these are not reported in literature.¹⁵ The authors suggest publication of these T-scores in order to let future studies be able to compare the QoL of their population of children with CP to an European standard.

CONCLUSION

This study describes the QoL profile of 80 children with CP living in the Southern part of the Netherlands as measured by means of the by-proxy version of the KIDSCREEN-52. The children studied are reported to have relatively low QoL in the physical well-being, social support & peers, and social acceptance domains, but relatively high QoL in the parent relation & home life and the school environment domains. These findings provide a better understanding of the QoL of Dutch children with CP. They can be used to inform caregivers and service-providers and to focus health programs aiming to increase QoL in this group of children towards identified problem domains.

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CHAPTER X

GENERAL DISCUSSION AND CONCLUSION

GENERAL DISCUSSION

Topic specific discussions can be found at the end of each chapter. This general discussion will focus on three issues encountered repeatedly while writing this thesis. The first issue is the problems and dilemmas associated with measuring concepts. The second issue is the rationale of evaluating your outpatient clinic. The third and final issue is the surplus value of qualitative research.

MEASURING CONCEPTS

During this thesis attempts have been made to measure several concepts, i.e. QoL and psychosocial adjustment. Concepts are inventions of the human mind to construct a model of the world.¹ They are abstract and cannot be touched, felt, or seen. Nevertheless, the significance of concepts like QoL and psychosocial adjustment is widely recognized. Therefore, these abstract and unobservable concepts have to be translated into something concrete and measurable. This process is called operationalisation and requires several criteria with regard to validity, consistency, stability, and reliability to be met.² Fortunately, the KID-SCREEN group Europe and Stein & Jessop have already done this and provided the clinician / researcher with valid and reliable tools to measure QoL (KID-SCREEN) and psychosocial adjustment (PARS-III) respectively.^{3, 4} However, results found still have to be interpreted with caution and considerable knowhow. Let us take the concept of QoL. QoL is defined as “an individual’s perception of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns”.⁵ In a very large, comprehensive, multi-centre study published in the *Lancet* it was concluded that the QoL of children with CP is similar to that of other children on all domains.⁶ The authors stated that pity and sorrow are therefore not in place. Another study investigated QoL of child and adolescent retinoblastoma survivors and found that their QoL is comparable to the general population with even significantly higher QoL on the moods & emotions and the autonomy domains.⁷ Does this mean that the QoL of a child with CP fighting has spastic movements in his wheelchair is similar to that of his brother outside playing soccer and that we should wish for everybody to get retinoblastoma? Probably not. It most likely means that determinants of QoL have shifted in children with CP and that surviving retinoblastoma makes people more aware of certain domains of QoL when approached by a researcher interested in their QoL. Furthermore, admitting that your or your child’s QoL is below average is a hard thing to do. The psychological effects when asked to judge your own or your child’s QoL have not yet been studied. However, indirect evidence for a biased representation of one’s own QoL comes from studies on self-presentation

and narcissism on facebook, the planets largest social networking platform today. It is repeatedly found that people tend to self-promote and over-represent their lives.⁸⁻¹¹

In my opinion two aspects of concepts like QoL and psychosocial adjustment are the most useful and the most interpretable: 1) the profile expressed in different domains; 2) the development over time.

Studying the domains of QoL in a population of patients may expose problem areas which could lead to treatment options. In our KIDSCREEN study on the QoL of Dutch children with CP (chapter IX) we found that these children are reported to have significantly higher QoL on the school environment and parent relation & home life domains and significantly lower QoL on the social support & peers and social acceptance domains. This observation leads to the assumption that Dutch people committed to these children (parents, family, teachers) have a significant positive contribution to their QoL, while non-committed others (peers) might negatively influence their QoL. These results are in accordance with the results obtained in our PARS-III study on psychosocial adjustment in Dutch children with CP (chapter III) in which we found low scores on the peer relations domain of psychosocial adjustment. It therefore makes sense to focus future health programs aiming to raise QoL in children with CP towards improving peer relations and social acceptance of these chronically impaired children.

The development of QoL over time was also studied in this thesis. This was done in children with CP who received an ITB pump in order to treat intractable spasticity (chapter VIII). It was shown that the positive effects on pain, ease of care, and mental health identified in the first year after commencement of treatment are still present today. Moreover, additional benefits have appeared, e.g. significantly improved scores on the Parent Impact – Emotional and the Parent Impact – Time subscales of the CHQ. According to the CHQ manual this means that care-givers experience fewer feelings of emotional worry / concern and fewer limitations in time available for personal needs due to the child's physical and / or psychosocial health.¹² It is difficult to tell whether this is a direct result of ITB therapy or whether this would also occur in parents with children not receiving ITB therapy. An ever growing amount of experience in caring for their children could explain the decrease in worries and concern and the increase in time for personal needs of the care-givers.

Another additional benefit was present 6–9 years after pump implantation, i.e. significantly improved scores on CHQ PhS. The subscales that contribute most profoundly to the PhS are physical functioning, role/social limitations (physical), bodily pain/discomfort, and general health.¹² It appears that improvements in CHQ PhS need more than 12 months to become evident (figure 8.2). A possible explanation for this observation is that improvements in terms of CHQ PhS require more than a reduction in spasticity alone. New possibilities have to be explored and practiced, which takes some time. On the other hand, a

reduction in spasticity will cause an immediate effect on pain and ease of care (figure 8.2).

EVALUATING YOUR OUTPATIENT CLINIC

Part of this thesis could be interpreted as a so-called audit. An audit measures clinical practice against current standards. It is a slightly odd type of research. Instead of searching for the right thing to do, it is checked whether or not the right thing is being done. In the United Kingdom it is standard practice for young doctors to perform an audit while in their foundation years.¹³ An audit serves multiple purposes. A cochrane review concluded that an audit can improve the practice of health care professionals.¹⁴ Furthermore, in these times where there is both an increasing demand on clinicians to implement evidence based medicine and optimize health care interventions routinely as an increasing pressure to rationalize treatment costs, evaluating your outpatient clinic seems a logical thing to do. The main problem, especially when treating severely handicapped children, is the lack of a quick, simple, and meaningful outcome measure. For example, it is not reasonable to expect clinicians to evaluate all children with CP receiving BTX-A injections by means of the PEDI, which takes over 1 hour per session.

During this thesis a VAS was used multiple times for different purposes. It was, along with other more sophisticated and time-consuming instruments, used to evaluate the effects of BTX-A treatment, ITB treatment, and RF-DRG treatment in children with CP. In chapter VI we showed that a VAS was able to measure effect of BTX-A treatment and that overall correlations with standard evaluation instruments were in the expected direction. Besides being a quick and easy method for evaluating treatment in a busy outpatient setting, the VAS is a subjective measure of the effects that treatment has on individually chosen goals. We would like to argue that it is this subjective nature of the VAS that makes it very suitable to evaluate treatment effects in children with CP at the severe end of the spectrum. Expecting to measure functional gain after treatment is not realistic in these children and most of the times is not the desired treatment goal set by the child and his caregivers. Usually the child and his caregivers are the best judges of the impact that the treatment has had on the daily life of the child. Furthermore, it is known that caregivers of children with profound impairments note changes in function far more accurately than staff workers. Small changes, noticed by caregivers but not picked up by conventional outcome measures, can add significant improvement to lives of children with CP and their caregivers.

Using this subjective VAS and other more objective and time-consuming instruments (Tardieux, MAS, CHQ, KIDSCREEN) we found evidence supporting the use of BTX-A, ITB, and RF-DRG treatment in the population of children with CP

seen at the outpatient clinic of the MUMC. These results verify the methods used to treat children in this university hospital. Furthermore, caregivers and children with CP can now be informed about the anticipated effects of several treatments not only based on data reported in literature but also based on results obtained by the local multidisciplinary CP working group.

QUALITATIVE RESEARCH

Traditionally, research in medicine has been quantitative by nature. These studies consist of identifying a problem, formulating a hypothesis, conducting an experiment, followed by supporting or dismissing the hypothesis. This is considered true research by many.

However, over the last decade there has been increasing interest for qualitative research. Boyd described qualitative research as broadly stated questions about human experiences and realities studied through sustained contact with persons in their natural environment, and producing rich, descriptive data that aid in understanding those person's experiences.¹⁵

Although qualitative studies have not been performed as part of this thesis, they have been very useful in the interpretation of data found. This was particularly true for the KIDSCREEN study (chapter IX). In this study we assessed the QoL of all children with CP living in the Southern part of the Netherlands. Bearing in mind the severity of CP in these children, we were forced to use the by-proxy version of the KIDSCREEN-52. Using this generic QoL instrument it was found that children with CP living in the Southern part of the Netherlands are reported to have significant lower QoL on three domains: physical well-being, social support & peers, and social acceptance. Less QoL on the physical well-being domain makes sense considering the GMFCS levels, the frequency of reported pain, and the accompanying impairments in these children. However, interpreting the results on the social support & peers and social acceptance domains posed somewhat of a problem, especially since these data were reported by care-givers. In other words, a QoL problem was identified however possible explanations for this observation were lacking. We came up with two possible, non-exclusive explanations: one based on quantitative research, the other on qualitative research. With regard to the first, in a large, cross-sectional survey study using the KIDSCREEN-52 among 16.210 children in children and adolescents 8–18 years of age in 11 European countries, Analitis et al found that living in the Netherlands holds the highest odds ratio (1.68) of being bullied.¹⁶ These results could explain why more Dutch children with CP than usual feel tormented, bullied, and rejected by peers. The second explanation is based on qualitative research by Parkinson et al who investigated the extent of agreement between children with CP and their caregivers concerning their views on what contributed to the children's QoL.¹⁷ They conducted qualitative interviews with

26 children with CP and 35 caregivers and came to the conclusion that there is considerable overlap but also some divergence. For example, children reported enjoying being on their own from time to time, while caregivers tended not to value these attitudes and put considerable effort into engineering opportunities for their child to be included socially. The interviewers found them very concerned about their child's experiences of being isolated or bullied by other children, often emphasizing this more than the children themselves. In other words, it is very well possible that low QoL on the social support & peers and social acceptance domains is due to concerns of the caregivers rather than what the children experience themselves. This is in accordance with our PARS-III study (chapter III) in which it was shown that children with CP psychosocially adjust to their motor and accompanying problems by withdrawal, without establishing sufficient and comprehensive peer relations. The question remains: who is right? Is it acceptable for children with CP to withdraw and enjoy time spent on their own, or are the caregivers right by stating that the children underestimate the risk and consequences of being socially isolated and that effort has to be put into engineering opportunities for their child to be included socially? Again, this highlights the necessity of measuring concepts like QoL and psychosocial adjustment through time as this would show the long-term consequences of withdrawal and the lack of social support in these children.

Another surplus value of qualitative research will be discussed. As already stated before, measuring treatment effect in children with CP poses somewhat of a challenge. Expecting large improvement in severely impaired children is unfortunately most often not realistic. However, small improvements, no matter how little, can make a huge difference. Against this background the following example is discussed.

In our long-term follow-up study on the effects of ITB treatment on intractable spasticity in children with CP (chapter VIII), multiple evaluation instruments were used. Among others, these included the CHQ, the KIDSCREEN, three self-made questionnaires (pain, function, complications, surgeries, hospitalizations, outpatient clinic visits), the Lifestyle Assessment Questionnaire for CP (LAQ-CP), the PARS-III, the CBCL and the SEV (manuscript in preparation). For one child treated with ITB only minimal improvements on all of these instruments were reported by the caregivers. However, when asked if they would choose for ITB treatment for their child again, considering the advantages (effects) and disadvantages (surgeries, complications, outpatient visits, and hospitalizations) experienced over all those years, they were absolutely positive. They stated that the slight increase in the range of leg abduction, improved ease of care and dressing dramatically. Thus, in this case a qualitative interview shed an entirely different light on results obtained by quantitative research.

CONCLUSION

In this thesis several clinical and therapeutic aspects of CP have been studied. The psychosocial adjustment (chapter I) and QoL (chapter IX) of children with CP seen at the outpatient clinic of the MUMC were investigated. Conventional treatments, like BTX-A (chapter IV) and ITB (chapter VI), and their complications (chapter V) have been evaluated and their effectiveness was confirmed. Furthermore, new treatments, like RF-DRG (chapter II) and Levetiracetam (chapter III), have been researched and found promising. The main message of this thesis is the following. When treating children with CP it is essential to understand their way of coping with their often severe disabilities and limitations and how this influences their QoL. Subsequently, treatment goals have to be set that are both obtainable and desired by both the child and his caregivers. Not only does one have to select the right treatment option, but also the right evaluation method.

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ENGLISH SUMMARY

This thesis addressed clinical and therapeutic aspects of cerebral palsy (CP). Several aspects of overall assessment, treatment, and its evaluation were studied in the population of children with CP seen at the outpatient clinic of the Maastricht University Medical Centre (MUMC).

CP is a major health problem as it affects 1 in 400 children making it the most common developmental disorder associated with lifelong disability. It is defined as a static, but often changing disorder of movement and posture due to a defect or lesion to the developing fetal or infant brain. In addition to their motor problems, children with CP often have impairments of learning, hearing, vision, and communication and frequently have seizure disorders. As a first step of this thesis a study was performed to see how these children adjust to their often severe disabilities and limitations. Therefore, in **chapter III** the psychosocial adjustment of children with CP is described. The main problem in this research area is that there are few standardized instruments specifically developed to assess psychosocial adjustment in children with a chronic illness. One very suitable instrument but not previously used in children with CP is the Psychosocial Adjustment and Role Skills Scale - III (PARS-III). The parents of all 94 children with CP (aged 4–18 years) seen at the outpatient clinic of the MUMC were informed about the study and asked to participate. All except one agreed and were sent the PARS-III questionnaire. The 93 children with CP consisted of 59 boys and 34 girls with a mean age of 12.3 years (SD 3.8; 4–18). Forty-four per cent of the children with CP were wheelchair dependent and 52% had a cognitive level below 70. Ninety-five healthy children and 63 boys with Duchenne Muscular Dystrophy (DMD) were used as reference groups. As the PARS-III had never before been applied to children with CP, its use had to be justified first. Results showed good internal consistency for the total PARS-III score: an alpha of 0.89. Confirmatory Factor Analysis confirmed the six domains of psychosocial functioning on the PARS-III questionnaire in children with CP. Based on these results the PARS-III scores of children with CP were investigated. It was found that they achieve significantly lower psychosocial adjustment scores when compared to healthy children ($p = 0.00$), especially on the domains peer relations ($p = 0.00$), anxiety/depression ($p = 0.00$), withdrawal ($p = 0.00$), and productivity ($p = 0.02$). Overall, they did not differ significantly from boys with DMD ($p = 0.93$), however, they scored significantly lower on the domain peer relations ($p = 0.03$).

It was found that the patient characteristics most predictive for lower PARS-III domain and total scores were less gross motor function, a lower level of hand function, less communication skills, and bilateral spastic CP. Put together in a model, these four patient characteristics could explain a significant proportion (36%) of the variation in PARS-III total scores.

It was concluded that the PARS-III questionnaire for parents can be used in children with CP. Using this questionnaire, it was found that children with CP

achieve lower psychosocial adjustment scores when compared to healthy children, especially in the domains peer relations, anxiety/depression, withdrawal, and productivity. It was suggested that a better understanding of why and when children with CP develop psychosocial maladjustment could lead to opportunities to alter the course of coping and therefore improve their quality of life (QoL).

The most common motor problem in children with CP is spasticity. Besides intrathecal Baclofen (ITB), selective dorsal rhizotomy (SDR) is one of the most commonly performed neurosurgical procedures. As multi-level laminectomies at the L1-S1 level are often required, the procedure is invasive and can lead to complications as transient urinary incontinence, chronic low back pain, and spinal deformity. Furthermore, considerable cooperation of the patient is required to successfully complete the postoperative rehabilitation program. We hypothesized a percutaneous radiofrequency lesion of the dorsal root ganglion (RF-DRG) to be a simple and safe alternative treatment. In **chapter IV** the pilot study undertaken to test this hypothesis is reported. The RF-DRG treatment was considered by the multi-disciplinary spasticity management team of the MUMC in children with severe hip flexor / adductor spasms accompanied by pain and / or care giving difficulties. During this pilot study a total of 19 RF-DRG procedures were performed in 17 children.

The first six children were systematically evaluated at baseline, and 1 month and 6 months after treatment by means of the Modified Ashworth Scale (MAS), the Gross Motor Function Measure (GMFM), and a caregiver's questionnaire. An improvement in muscle tone after RF-DRG was identified on both the short (1 month) and long (6 months) term using the MAS. No functional improvement on the GMFM could be detected. Using the caregiver's questionnaire, improvements in ease and quality of care and pain were found.

The following 11 children were evaluated at 6 weeks and 3 months after intervention using a Visual Analogue Scale (VAS), which was used to measure change on individually formulated treatment goals. We changed the evaluation methods, as we were not able to detect the kind of change that the caregivers unanimously did notice. Furthermore, studies were being published that showed that the MAS and the GMFM are not suitable to measure changes in these severely handicapped children. The VAS scores showed improvement on most of the defined treatment goals in most children. Most parents reported that the positive effects of the RF-DRG lasted at least 6–9 months.

It was concluded that RF-DRG is a promising new treatment option for severe spasticity in children with CP. The main advantages are its less invasive character compared to the SDR with the potential benefit of a shorter hospitalization period, and its clear pain-reducing effect. We suggested a randomized controlled trial to define its definitive effectiveness.

Less common than the spastic subtype of CP is the dyskinetic subtype. Its pathophysiology is not fully elucidated, but existing evidence suggests that dysfunction of the basal ganglia (BG) plays a role in this entity. As with most diseases in which the causes are not yet fully understood, the symptomatic treatment of this movement disorder remains very difficult. Several anticonvulsants seem to be efficacious for the treatment of (paroxysmal) involuntary movement disorders. On the basis of a recent report about Levetiracetam (LEV) efficacy in the treatment of movement disorders, we started LEV in two female patients (aged 5 and 8 years) with dyskinetic CP unresponsive to conventional drugs mostly used in such cases. These 2 cases are described in **chapter V**. Both patients experienced severe perinatal asphyxia and subsequently developed dyskinetic CP, clinically characterized by choreoathetosis. Neuropsychological testing of these children showed a low average developmental quotient and no attentional deficits. Monotherapy with LEV was initiated to improve balance control and fine motor skills. Treatment was evaluated by use of video analysis and VAS. In both children an impressive improvement of balance control and fine motor skills was observed. No side-effects occurred. Furthermore, both patients showed more interest for and pleasure during activities according to their parents. During multidisciplinary evaluations of the initiated therapy, the parents, the therapist, and the rehabilitation doctor all confirmed that the effect initially observed was still present at 14 respectively 26 months after commencement of therapy. This is the first report suggesting that LEV may be used as an alternative to treat unmanageable choreoathetosis of a non-progressive kind, e.g. in children with dyskinetic CP. This is important because choreoathetosis appears to be a very severe and disabling condition which is difficult to treat. This could partly be due to the differences in pathophysiology between the two aspects of the condition, i.e. athetosis can be treated by increasing dopaminergic activity in the BG, while chorea can be treated by decreasing dopaminergic activity. These findings and our results suggest that LEV might reduce choreoathetosis by means of another pathway. So far, the synaptic vesicle protein SV2A has been identified as the binding site for LEV, but the molecular action of SV2A is still unknown.

Further and larger studies are needed to confirm the positive effects of LEV on choreoathetosis in patients with a non-progressive, non-paroxysmal, dyskinetic movement disorder.

When treating children with CP, evaluation of treatment is essential. Furthermore, there is an increasing need for clinicians to evaluate their daily clinical practice. One of the most commonly performed treatments in children with CP is Botulinum toxin A (BTX-A) injections to reduce spasticity. The main problem is that there is no simple, quick, and useful outcome measure available to evaluate these kinds of treatments. In spite of its clear limitations, the standard clinical scale for measuring spasticity remains the Ashworth Scale. However, the Ashworth Scale does not measure spasticity exclusively, it has low inter-rater reliability, and it lacks precision and sensitivity for measuring smaller changes

in spasticity. Although the GMFM is widely accepted as the best available quantitative measure for gross motor function in CP, it is of limited value when assessing functional benefits in severely affected children. In **chapter VI** we hypothesized that a simple VAS could be a quick and useful tool to evaluate the effects of BTX-A injections on spasticity in daily clinical practice. Therefore, we prospectively collected data on 55 children with CP (25 males; 30 females) with a mean age of 8.3 years (SD 3.3) who were carefully selected by a multi-disciplinary team of specialists to be treated with BTX-A injections. Goals for BTX-A treatment were defined in close consultation with the parents / caregivers and the children themselves. Treatment goals were improvement of pain, problems with nursing, sitting position, standing, and walking. On the day of the intervention, the caregivers were asked to score the present situation for the selected treatment goals on a VAS (0 = very satisfied; 10 = very dissatisfied). VAS scores and side-effects were assessed at follow-up 6 and 12 weeks after treatment. Furthermore, for children who were able to walk three clinical examinations of tone (passive range of motion (PROM), angle of catch (AOC), and the Modified Tardieu) were performed for the hamstrings and gastrocnemius muscles.

Seventy-four interventions were performed in 55 children. The most frequently formulated goal was improvement of walking (56 times), followed by improvement of nursing (24 times) and improvement of standing (15 times). A statistically significant effect was found for improvement of care ($p \leq 0.00$), standing ($p \leq 0.00$), and walking ($p \leq 0.00$). No statistically significant effect was found for pain ($p = 0.18$), probably because of small numbers. The VAS was positively but not significantly correlated to the PROM for both muscle groups and to the AOC for the hamstrings. There was a negative but not significant correlation between the VAS and the AOC of the gastrocnemius. The Modified Tardieu was positively correlated to the VAS for all muscles investigated and significant for the left gastrocnemius. In 36 of the 74 (48.6%) interventions a positive effect was observed for more than 12 weeks.

We concluded that a VAS was able to measure treatment effect and that overall correlations with standard evaluation instruments were in the expected direction. Evaluating spasticity treatment with the use of the VAS has several important advantages. Firstly, it is a quick and easy method for evaluating treatment in an outpatient setting, in which time-consuming evaluations are not an option and where there is a need for these kinds of instruments. Secondly, it is a subjective measure of the effects that BTX-A treatment has had on individually chosen goals. Usually the patient and his/her caregiver(s) are the best judges of the severity of the spasticity, as they are the only people who can assess its impact on the daily life of the patient.

Besides evaluating the effect of BTX-A treatment on spasticity, the clinician has to be aware of possible side-effects. In the group of 55 children described in chapter VI side-effects were observed 7 times in five children treated with BTX-

A injections. One of those side-effects was constipation. **Chapter VII** describes this up until now unknown side-effect of BTX-A treatment in this and two other patients treated with BTX-A injections. Constipation was observed within the first week of BTX-A treatment. In all three cases, this symptom resolved completely and almost simultaneously with disappearance of the therapeutic effects of BTX-A. Two patients received a second treatment and both presented the same autonomic cholinergic remote symptoms. The third patient refused a second treatment due to the side-effect noted earlier.

As the colon is not in close proximity to the injection sites, the constipation is most likely caused by a systemic effect of BTX-A. This presumption was made even more likely after electromyography (EMG) of the hypothenar muscles while stimulating the ulnar nerve at the wrist in 1 patient. The amplitude of the initial response was normal, but after prolonged 3 Hz stimulation a slight decrementing response occurred. An average of 11% decrement in amplitude was visible from sixth to eighth compound muscle action potentials. This indicates that fewer muscle fibers than normal responded to nerve stimulation during a train of stimuli, i.e. due to generalized blockage of acetylcholine release in nerve terminals.

We concluded that familiarity with this autonomic systemic side-effect of BTX-A is essential for clinicians treating patients already at risk for gastrointestinal dysfunction. Because the adverse effects were treatable and transitory, we suggested that constipation per se is not an absolute contra-indication, if from a therapeutic point of view, BTX-A is indicated.

Another, not yet discussed treatment option in the management of spastic CP is ITB therapy. A couple of years ago, Hoving et al performed methodologically well-designed studies on ITB therapy in 17 children with intractable spastic CP. Follow-up showed positive effects on pain, ease of care, and mental health to be present 1 year after pump implantation.

However, long-term results of ITB therapy in children with intractable spastic CP are still limited, especially with regard to outcomes relevant to the patient and his / her caregivers. Therefore, we re-evaluated these 17 patients 6–9 years (mean 7.5 years, SD 0.9) after commencement of treatment. The results can be found in **chapter VIII**.

The parents of these 17 children (9 girls, 8 boys; mean age 21.1 years, SD 3.1, 14–25; GMFCS level 3: n = 1, level 4: n = 2, level 5: n = 14) filled out the Child Health Questionnaire (CHQ), current satisfaction on the VAS regarding previous set treatment goals, a questionnaire concerning functioning of their child, and a self-made questionnaire.

It was found that the CHQ and VAS scores had not changed significantly since 12 months post-implantation. The positive effects on pain, ease of care, and mental health were still present. Moreover, additional benefits had ap-

peared i.e. significantly improved scores on the Parent Impact – Emotional subscale, Parent Impact – Time subscale, and the Physical Summary.

Although it seems that the effects eventually stabilize, minimal improvement can still be expected 12 months after pump-implantation, especially for individually defined treatment goals. Furthermore, it appears that improvements in terms of physical QoL (CHQ PhS) need more time to become evident. At 12 months post-implantation there was no statistically significant difference compared to baseline ($p = 0.16$); however, at present there is ($p = 0.02$).

Regardless of the side-effects, the complications, and the necessity of eventually substituting the pump, 94% of the care-givers would choose ITB therapy for their child again.

We concluded that this study confirmed the long-term beneficial effects of ITB-therapy in children with intractable spastic CP and should be considered as a first step towards studies with even longer and more extensive follow-up.

So far the emphasis of this thesis has been on the treatment and its evaluation of motor problems in children with CP. However, children with CP are often faced with a broad spectrum of accompanying problems, e.g. impairments of learning, hearing, vision, communication, sleep, sexual functioning, and seizure disorders. There is increasing interest in the consequences of the combination of motor problems and these accompanying problems on the QoL of these children with CP. Therefore, in **chapter IX** the QoL of all children with CP aged 8–18 years seen at the outpatient clinic is described.

Acting upon the largest study on QoL of children with CP so far (Study of Participation of Children with CP Living in Europe (SPARCLE), 7 European countries), we used the same QoL instrument, i.e. the KIDSCREEN-52. This is a modern, generic QoL instrument, which uses questions based on focus-groups with children and adolescents all over Europe. The KIDSCREEN-52 focuses entirely on subjective perceptions, has shown to possess excellent psychometric properties, can be used for both disabled and non-disabled children, and can be reported by both the children themselves and their caregivers.

The parents of all 81 children with CP aged 8–18 years seen at the outpatient clinic of the MUMC, were informed about the study and the parents of 80 children (31 girls, 49 boys; mean age 13.4 years, SD 2.98; 44% wheelchair dependent; 55% cognitive levels below 70) were willing to participate. T-scores were used to compare the QoL of Dutch children with CP to the QoL of over 15.000 children from the general European population. It was found that Dutch children with CP are reported to have relatively low QoL in the physical well-being, social support & peers, and social acceptance domains, but relatively high QoL in the parent relation & home life and the school environment domains. For the physical well-being domain it was found that higher GMFCS level was associated with lower T-scores. Less communication skills and lower cognitive levels were associated with lower T-scores in the social support & peers and school

environment domains. Furthermore, parents with no educational qualification rated their child's QoL in the parent relation & home life higher. For the social acceptance domain no associated factors could be identified.

We found it intriguing to see that these Dutch children with CP are reported to have significantly higher QoL in the school environment and parent relation & home life domains and significantly lower QoL in the social support & peers and social acceptance domains compared to a sample of European children from the general population. We came up with two possible, non-exclusive explanations for this pattern not observed in the European population of children with CP. First of all, living in the Netherlands holds the highest odds ratio of being bullied and this could explain why more Dutch children with CP than usual feel tormented, bullied, and rejected by peers. Secondly, qualitative research has shown that children with CP enjoy being on their own from time to time. This is in accordance with our PARS-III study (chapter III) in which it was shown that children with CP psychosocially adjust to their motor and accompanying problems by withdrawal, without establishing sufficient and comprehensive peer relations. Caregivers do not appreciate these attitudes and put substantial effort into creating opportunities for their child to be included socially. In other words, it is very well possible that low QoL on the social support & peers and social acceptance domains is due to concerns of the caregivers rather than what the children experience themselves.

We concluded that these findings provide a better understanding of the QoL of Dutch children with CP and that they can be used to inform caregivers and service-providers, and to focus health programs aiming to increase QoL in this group of children towards identified problem domains.

NEDERLANDSE SAMENVATTING

Dit proefschrift beschrijft klinische en therapeutische aspecten van cerebrale parese (CP). Verschillende aspecten van behandeling en evaluatie werden bestudeerd in de populatie kinderen met CP die gezien wordt op de polikliniek van het Maastricht University Medical Centre (MUMC).

CP is een groot gezondheidsprobleem. Het wordt gezien bij 1 op de 400 nieuwgeborenen waardoor het de meest voorkomende ontwikkelingsstoornis is die gepaard gaat met levenslange handicaps. De definitie van CP stelt dat het een niet-progressieve bewegings- en houdingsstoornis is t.g.v. schade aan het zich ontwikkelende brein van de foetus of het jonge kind. Naast motorische problemen ontwikkelen kinderen met CP vaak leerstoornissen, epileptische stoornissen en problemen ten aanzien van het gehoor, visus of communicatie.

Als eerste onderdeel van dit proefschrift werd gekeken hoe deze kinderen omgaan met hun vaak ernstige handicaps en beperkingen. In **hoofdstuk III** wordt de psychosociale aanpassing van kinderen met CP beschreven. Het grootste probleem in dit onderzoeksgebied is dat er maar weinig gestandaardiseerde instrumenten zijn die specifiek ontwikkeld zijn om psychosociale aanpassing bij kinderen met een chronische aandoening te onderzoeken. Een zeer geschikte, maar nog niet eerder voor kinderen met CP gebruikte vragenlijst is de Psychosocial Adjustment and Role Skills Scale III (PARS-III). De ouders van alle 94 kinderen (4–18 jaar oud) die gezien worden op de polikliniek van het MUMC werden gevraagd om deel te nemen aan de studie. Op één na gaven alle ouders toestemming en kregen de PARS-III vragenlijst toegestuurd. De groep van 93 kinderen bestond uit 59 jongens en 34 meisjes. De gemiddelde leeftijd bedroeg 12.3 jaar (SD 3.8; 4–18). Vierenveertig procent van de kinderen was rolstoelgebonden en 52% had een cognitief niveau onder de 70. Als referentie werd de psychosociale aanpassingsdata van 95 gezonde kinderen en 63 jongen met Duchenne's Musculaire Dystrofie (DMD) gebruikt. Omdat de PARS-III vragenlijst niet eerder gebruikt werd voor kinderen met CP, moest in eerste instantie het gebruik ervan gerechtvaardigd worden. Testen lieten een goede interne consistentie zien: een Cronbach's alfa van 0.89. Confirmatory Factor Analysis bevestigde de 6 domeinstructuur van de PARS-III vragenlijst wanneer deze gebruikt wordt voor kinderen met CP. Vervolgens konden de PARS-III scores van kinderen met CP bestudeerd worden. Er werd gevonden dat ze lager scoorden qua psychosociale aanpassing dan gezonde kinderen ($p = 0.00$), m.n. op de domeinen "peer relations" ($p = 0.00$), "anxiety/depression" ($p = 0.00$), "withdrawal" ($p = 0.00$) en "productivity" ($p = 0.02$). Over het algemeen verschilden de kinderen met CP niet van jongens met DMD ($p = 0.93$). Echter, wanneer men kijkt naar de verschillende domeinen van psychosociale aanpassing, scoorden de kinderen met CP significant lager dan jongens met DMD op het domein "peer relations" ($p = 0.03$). Middels univariate en multivariate (forward entry, dummy variables) regressie analyse werd gevonden dat grove motorische functie, mate van hand-

functie, communicatie kunde en bilaterale CP de patiëntkarakteristieken waren met de grootste associatie met PARS-III scores. Wanneer men deze 4 patiëntkarakteristieken samen in een regressiemodel zet, kan een significant gedeelte (36%) van de variatie in PARS-III scores verklaard worden.

De conclusie luidde dat de PARS-III vragenlijst voor ouders bruikbaar is voor het meten van psychosociale aanpassing in kinderen met CP. Middels deze vragenlijst toonden wij aan dat kinderen met CP lager scoorden qua psychosociale aanpassing dan gezonde kinderen, m.n. op de domeinen “peer relations”, “anxiety/depression”, “withdrawal” en “productivity”. Een beter begrip van onjuiste psychosociale aanpassing kan mogelijkheden bieden tot het optimaliseren van copingsmechanismen bij deze kinderen met een chronische aandoening. Dit kan vervolgens bijdragen aan een betere kwaliteit van leven (QoL).

Het meest voorkomende motorische probleem bij kinderen met CP is spasticiteit. Indien er sprake is van ernstige spasticiteit, kan neurochirurgisch ingrijpen noodzakelijk zijn. Naast intrathecale Baclofen (ITB) behandeling, is selectieve dorsale rhizotomie (SDR) één van de meest uitgevoerde neurochirurgische procedures. Hierbij zijn vaak laminectomieën op meerdere niveaus van L1-S1 nodig en tevens bestaat er een aanzienlijk risico op tijdelijke urine incontinentie, chronische lage rugpijn en spinale deformiteiten. Verder is er een aanzienlijke medewerking van de patiënt nodig om het intensieve post-operatieve revalidatietraject succesvol te doorlopen. Wij veronderstelden dat een percutane radiofrequente laesie van het achterste wortel ganglion (RF-DRG) een simpel en veilig alternatief zou kunnen vormen voor SDR. In **hoofdstuk IV** wordt deze hypothese getoetst middels een pilot studie. Een RF-DRG behandeling werd door de multi-disciplinaire spasticiteitswerkgroep van het MUMC overwogen bij kinderen met ernstige heup flexor / adductor spasmes die gepaard gingen met pijn of moeilijkheden rondom de verzorging. Uiteindelijk werden gedurende deze pilot studie bij 17 kinderen 19 RF-DRG behandelingen uitgevoerd. De eerste 6 kinderen werden systematisch geëvalueerd vlak voor de start van behandeling en 1 en 6 maanden na behandeling. Evaluatie geschiedde middels de Modified Ashworth Scale (MAS), de Gross Motor Function Measure (GMFM) en een zelfde gemaakte vragenlijst voor verzorgers. De MAS liet een verbetering van spiertonus na RF-DRG behandeling zien op zowel de korte (1 maand) als de lange (6 maanden) termijn. Op het gebied van functie kon geen verbetering worden gevonden middels de GMFM. De zelfgemaakte vragenlijst voor verzorgers liet een verbetering zien in het gemak en de kwaliteit van verzorging en een vermindering van pijn.

De volgende 11 kinderen werden geëvalueerd middels een Visual Analogue Scale (VAS). Deze werd voor aanvang van de behandeling en vervolgens 6 weken en 3 maanden na behandeling gescoord voor individueel gestelde behandeldoelen. Wij achtten deze verandering van evaluatiemethode noodzakelijk daar we met behulp van de gebruikte evaluatie instrumenten niet in staat waren

de effecten van behandeling te detecteren die de verzorgers van deze kinderen unaniem wel aangaven. Daarbij kwam dat er in de literatuur studies verschenen die lieten zien dat de MAS en de GMFM niet geschikt waren om effect van behandeling te evalueren bij deze groep van ernstig gehandicapte kinderen. De VAS scores lieten verbetering zien bij de meeste van de van tevoren vastgestelde doelen. Volgens het merendeel van de ouders waren de effecten de RF-DRG behandeling 6 tot 9 maanden later nog steeds aanwezig.

De conclusie naar aanleiding van deze pilot studie luidde dat RF-DRG een veelbelovende mogelijkheid is voor de behandeling van ernstige spasticiteit bij kinderen met CP. De grote voordelen zijn het minder invasieve karakter van RF-DRG t.o.v. SDR, een mogelijk kortere opnameduur en een duidelijk pijnverminderend effect. Een RCT is nodig om de definitieve plaats van RF-DRG bij de behandeling van spastische CP te bepalen.

Een subtype van CP dat minder vaak voorkomt dan spastische CP is dyskinetische CP. De pathofysiologie van dyskinetische CP is vooralsnog niet geheel opgehelderd. Huidige literatuur suggereert een dysfunctioneren van de basale ganglia (BG) als oorzaak voor de klinische symptomen. Net zoals als geldt voor andere ziektes waarbij de oorzaak onduidelijk blijft, is de symptomatische behandeling van deze bewegingsstoornis vaak erg moeilijk. Enkele anti-epileptica lijken werkzaam in de behandeling van (paroxysmale) onvrijwillige bewegingsstoornissen. Naar aanleiding van een recent case report over de werkzaamheid van Levetiracetam (LEV) bij bewegingsstoornissen, startten wij LEV bij twee meisjes (5 en 8 jaar oud) die niet reageerden op de conventionele medicatie voor dit type aandoening. Deze twee casussen worden beschreven in **hoofdstuk V**. Beide meisjes maakten perinataal ernstige asfyxie door en ontwikkelden vervolgens dyskinetische CP die klinisch gekenmerkt werd door choreoathetosis. Neuropsychologisch onderzoek van deze kinderen wees uit dat er sprake was van een laagnormaal ontwikkelingsniveau zonder aandachtsstoornissen. Monotherapie met LEV werd gestart om balans en fijne motoriek te verbeteren. Effect van behandeling werd geëvalueerd aan de hand van videoanalyse en VAS scores. Bij beide kinderen werd een indrukwekkende verbetering geconstateerd op het gebied van balans en fijne motoriek. Er traden geen bijwerkingen op. Verder gaven de ouders aan dat de kinderen meer interesse hadden gekregen voor activiteiten en hiervan ook meer plezier ondervonden. Tijdens een recente multidisciplinaire evaluatie van de therapie, 14 en 26 maanden na start van de medicatie, waren de ouders, de artsen en de fysiotherapeuten het met elkaar eens dat het effect van behandeling nog steeds aanwezig was.

Dit zijn de eerste twee casussen die suggereren dat LEV mogelijk een alternatieve behandelingsmogelijkheid is voor non-progressieve choreoathetosis, zoals die bij kinderen met dyskinetische CP. Dit is belangrijk daar choreoathetosis een sterk invaliderende en moeilijk te behandelen aandoening is. Dit is mogelijk terug te voeren op de verschillen in pathologie tussen de twee aspecten van het

ziektebeeld. Athetosis kan namelijk verminderd worden door dopaminerge activiteit in de BG te verhogen, terwijl chorea verminderd kan worden door dopaminerge activiteit in de BG juist te verlagen. Deze bevindingen en de door ons beschreven casussen suggereren dat LEV choreoathetosis mogelijk middels een andere pathway vermindert. Men heeft de bindingsplaats voor LEV inmiddels achterhaald (synaptic vesicle protein SV2A), echter het moleculaire werkingsmechanisme van dit eiwit is vooralsnog onbekend.

Toekomstige, goed opgezette studies zijn nodig om het positieve effect van LEV op choreo-athetosis bij patiënten met een non-progressieve, non-paroxysmale, dyskinetische bewegingsstoornis te bevestigen.

Wanneer men kinderen met CP behandelt, is evaluatie van deze behandeling essentieel. Hier bovenop komt dat er tegenwoordig onder dokters een grote behoefte aan het evalueren van hun dagelijkse klinische praktijk bestaat. Een van de meest uitgevoerde behandelingen bij kinderen met CP is het injecteren van Botulinum toxine A (BTX-A) met als doel spasticiteit te verminderen. Het grootste probleem is echter dat er geen simpele, snelle en zinvolle methode beschikbaar is om dit type behandelingen te evalueren. Ondanks zijn duidelijke beperkingen, wordt de Ashworth Scale voor dit doeleinde nog steeds het meest gebruikt. Echter, de Ashworth Scale meet niet enkel spasticiteit, heeft een lage inter-rater betrouwbaarheid en is niet in staat om kleine veranderingen in spasticiteit op te pikken. Ondanks dat de GMFM wereldwijd als beste kwantitatieve instrument wordt beschouwd voor het meten van grof motorisch functioneren, heeft deze maar beperkte waarde wanneer het gaat om ernstig beperkte kinderen. In **hoofdstuk VI** veronderstelden wij dat een simpele VAS een eenvoudig, snel en zinvol instrument zou kunnen zijn om de effecten van BTX-A behandeling van spasticiteit te evalueren. Om dit te onderzoeken verzamelden we prospectief data van 55 kinderen met CP (25 jongens; 30 meisjes) met een gemiddelde leeftijd van 8.3 jaar (SD 3.3) die zorgvuldig geselecteerd werden door een multi-disciplinaire spasticiteitswerkgroep om behandeling middels BTX-A injecties te ondergaan. Doelstellingen van behandeling werden samen met de ouders / verzorgers en de kinderen vastgesteld. De categorieën waarop verbetering werd nagestreefd betroffen pijn, verzorging, zitten, staan en lopen. Op de dag van behandeling werd aan de ouders / verzorgers gevraagd om op een VAS de huidige situatie per categorie te scoren. Hierbij betekende een score van 0 op de VAS dat de huidige situatie totaal niet problematisch was en een score van 10 dat de huidige situatie problematischer kon zijn. Zes en 12 weken na start van behandeling werden wederom VAS scores bepaald en werd er gekeken of er bijwerkingen waren opgetreden. Verder werd er voor kinderen die konden lopen 3 klinische onderzoeken van tonus verricht (passive range of motion (PROM), angle of catch (AOC) en Modified Tardieu) voor de hamstrings en de gastrocnemius spieren.

Bij 55 kinderen werden uiteindelijk 74 interventies verricht. Bij sommige kinderen werd van tevoren meer dan één doel gesteld. De meest geformuleerde doelstelling was het verbeteren van lopen (56 keer), gevolgd door het verbeteren van verzorging (24 keer) en verbeteren van staan (15 keer). Een statistisch significant effect van behandeling werd gevonden voor verbetering van verzorging ($p \leq 0.00$), staan ($p \leq 0.00$) en lopen ($p \leq 0.00$). Waarschijnlijk t.g.v. het kleine aantal patiënten bij wie vermindering van pijn werd nagestreefd, werd er geen significant effect voor deze doelstelling gevonden ($p = 0.18$). De VAS liet een positieve, maar statistisch geen significante correlatie zien met de PROM voor de twee spiergroepen en met de AOC voor de hamstrings. Er was sprake van een negatieve, maar statistisch geen significante correlatie tussen de VAS en de AOC voor de gastrocnemius. De Modified Tardieu was positief gecorreleerd aan de VAS voor de onderzochte spiergroepen en significant m.b.t. de linker gastrocnemius. In 36 van de 74 (48.6%) interventies werd geconstateerd dat het positieve effect van behandeling langer dan 12 weken aanhield.

We concludeerden dat een simpele VAS in staat was om effect van behandeling te meten en dat de correlaties met de conventionele evaluatie methoden in de te verwachten richting waren. Het evalueren van spasticiteit met gebruik van een VAS heeft een aantal belangrijke voordelen. Ten eerste is het een snelle en eenvoudige methode voor het evalueren van behandeling tijdens een poliklinisch spreekuur, waar ingewikkelde en tijdrovende evaluatiemethoden nu eenmaal geen optie zijn. Ten tweede meet een VAS op een subjectieve manier het effect van behandeling op vooraf gestelde doelen. Het is bekend dat de patiënt en zijn of haar ouders / verzorgers de beste beoordelaars zijn van de spasticiteit, daar zij de enige zijn die in staat zijn om de impact op het dagelijks leven in te schatten.

Naast het evalueren van het effect van BTX-A behandeling, moet de behandelend arts ook aandacht hebben voor mogelijke bijwerkingen. In de groep van 55 kinderen die beschreven wordt in hoofdstuk VI werden bij 5 kinderen in totaal 7 bijwerkingen geconstateerd na behandeling met BTX-A injecties. Bij één kind trad constipatie op als bijwerking. In **hoofdstuk VII** wordt deze vooralsnog onbekende bijwerking van BTX-A behandeling beschreven bij dit kind en nog 2 andere jongvolwassenen die ook behandeld werden met BTX-A.

Constipatie werd in alle 3 de gevallen binnen 1 week na behandeling geconstateerd. Deze bijwerking verdween uiteindelijk volledig en dit ging samen met het verdwijnen van de gunstige effecten van de BTX-A injecties. Twee patiënten ondergingen een tweede serie van BTX-A injecties en weer traden dezelfde autonome cholinerge bijwerkingen op. De derde patiënt weigerde een vervolgbehandeling i.v.m. de destijds opgetreden constipatie.

Het colon is niet nabij de injectieplaatsen gelegen en daarom is de constipatie het beste te verklaren als een systemische bijwerking van de BTX-A behandeling. Deze aanname werd nog waarschijnlijker gemaakt door het verrichten van

een EMG studie in 1 patiënt. Er werd een EMG gemaakt van de hypothenaire spieren terwijl de nervus ulnaris t.h.v. de pols gestimuleerd werd. De amplitudo van het initiële signaal was normaal, maar na langer durende stimulatie (3 Hz) trad een licht decrement in amplitudo op. Een gemiddelde van 11% decrement in amplitudo was zichtbaar van de zesde tot de achtste compound van actiepotentialen. Dit duidt erop dat minder spiervezels dan normaal reageren op een zenuwprikkel tijdens een reeks van stimuli. Oorzaak hiervoor is een algehele blokkade van acetylcholine vrijkomst in de zenuwuiteinden.

We concludeerden dat kennis van deze autonome en systemische bijwerking van BTX-A behandeling belangrijk is voor behandelaars van deze kinderen die sowieso al een grotere kans op gastro-intestinaal disfunctioneren hebben. Omdat de bijwerkingen goed te behandelen waren en van voorbijgaande aard bleken, stelden we voor dat constipatie an sich niet als absolute contra-indicatie beschouwd dient te worden in geval BTX-injecties therapeutisch geïndiceerd zijn.

Een andere, tot dusver niet besproken behandeloptie van spasticiteit bij kinderen met CP is ITB behandeling. Een aantal jaar geleden, verrichtten Hoving et al methodologisch zeer goed opgezette studies naar ITB behandeling bij 17 kinderen met CP met moeilijk behandelbare spasticiteit. Follow-up liet zien dat positieve effecten op pijn, verzorgingsgemak, and “mental health” nog steeds aanwezig waren 1 jaar na pomp-implantatie.

Echter, lange termijnsresultaten van ITB behandeling bij kinderen met CP met moeilijk behandelbare spasticiteit ontbreken vooralsnog. Daarom herevalueerden wij de 17 patiënten beschreven door Hoving et al 6–9 jaar (gemiddeld 7.5 jaar, SD 0.9) na start van behandeling. De resultaten staan beschreven in **hoofdstuk VIII**.

Aan de ouders van deze 17 kinderen (9 meisjes, 8 jongens, gemiddelde leeftijd 21.1 jaar, SD 3.1, 14–25; GMFCS level 3: n = 1, level 4: n = 2, level 5: n = 14) werd gevraagd verschillende vragenlijsten in te vullen, te weten de Child Health Questionnaire (CHQ), een functioneringsvragenlijst, een zelf gemaakte vragenlijst en hun huidige tevredenheid op een VAS m.b.t. de doelen gesteld voor aanvang van behandeling.

Eén ouder stuurde de CHQ niet terug. Alle overige data waren beschikbaar voor analyse.

Analyse liet dat CHQ en VAS scores niet significant veranderd waren t.o.v. de laatste evaluatie 12 maanden na pomp plaatsing. De positieve effecten op pijn, verzorgingsgemak en “mental health” waren nog steeds aanwezig. Bovendien waren er ook op andere schalen significante verbeteringen duidelijk geworden: de Parent Impact – Emotional subschaal, Parent Impact – Time subschaal en de Physical Summary.

Alhoewel het lijkt dat het behandel-effect na verloop van tijd stabiliseert, mag men toch ook nog 12 maanden na pomp plaatsing kleine verbeteringen verwachten, m.n. m.b.t. de individueel gestelde behandel-doelen.

Verder lijkt het erop dat verbetering op de Physical Summary meer tijd nodig had om tot stand te komen. Twaalf maanden na pomp plaatsing was er namelijk nog geen statistisch significant effect zichtbaar ($p = 0.16$), maar inmiddels wel ($p = 0.02$).

Ondanks de bijwerkingen, de complicaties, en de noodzaak om uiteindelijk de pomp te vervangen, zou 94% van de ouders / verzorgers opnieuw voor ITB behandeling voor hun kind kiezen.

Wij concludeerden dat deze studie de positieve effecten van ITB behandeling van kinderen met CP op de lange termijn bevestigt. Deze studie moet gezien worden als een eerste stap richting nog langere en uitgebreide follow-up studies.

Tot dusver heeft dit proefschrift zich gericht op de behandeling van motorisch problemen bij kinderen met CP en de evaluatie hiervan. Echter, kinderen met CP worden geconfronteerd met meer dan enkel motorische problematiek. Leerstoornissen, epileptische stoornissen, problemen met het gehoor, zicht of communicatie, slaapproblemen en seksuele problematiek zijn aan de orde van de dag. Er is de laatste jaren in de literatuur in toenemende mate belangstelling voor de gevolgen die deze combinatie van motorische en bijkomende problematiek heeft op de QoL van deze kinderen. Daarom wordt in **hoofdstuk IX** de QoL van alle kinderen met CP die gezien worden op de poli van het MUMC beschreven.

In navolging van de tot nu toe grootste studie naar de QoL van kinderen met CP (Study of Participation of Children with CP Living in Europe (SPARCLE), 7 Europese landen), gebruikten ook wij de KIDSCREEN-52 vragenlijst om QoL te meten. Dit is een moderne, generieke QoL vragenlijst die gebruik maakt van vragen die ontwikkeld zijn in focus-groups met Europese kinderen en jongvolwassenen. De KIDSCREEN-52 richt zich volledig op subjectieve percepties, heeft uitstekende psychometrische eigenschappen, kan gebruikt worden voor zowel geïnvalideerde als gezonde kinderen en kan door zowel kinderen zelf als door hun ouders ingevuld worden.

De ouders van alle 81 8–18 jarige kinderen met CP die gezien worden op de polikliniek van het MUMC werden geïnformeerd over de studie en de ouders van 80 kinderen (31 meisjes, 49 jongens; gemiddelde leeftijd 13.4 jaar, SD 2.98; 44% rolstoelgebonden; 55% cognitieve niveau onder de 70) waren bereid mee te doen. Er werd gebruik gemaakt van T-scores om de QoL van Nederlandse kinderen met CP te vergelijken met de QoL van meer dan 15.000 Europese kinderen van de algemene populatie. Het bleek dat volgens hun ouders Nederlandse kinderen met CP relatief laag scoorden op de domeinen “physical well-being”, “social support & peers” en “social acceptance”, terwijl ze juist hoog scoorden op de domeinen “parent relation & home life” en “school environment”.

Hogere GMFCS levels waren geassocieerd met lagere T-scores op het domein “physical well-being”. Minder communicatievaardigheden en een lager cognitief niveau waren geassocieerd met lagere T-scores op de domeinen “social support & peers” en “school environment”. Verder bleek dat ouders zonder vervolgopleiding hogere scores rapporteerden op het domein “parent relation & home life”. Geen van de onderzochte factoren waren geassocieerd met het domein “social acceptance”.

Het fascineerde ons om te zien dat, in vergelijking met de Europese kinderen van de algemene populatie, deze Nederlandse kinderen met CP volgens hun ouders significant hogere QoL hadden op de domeinen “school environment” en “parent relation & home life”, maar significant lagere QoL hadden op de domeinen “social support & peers” en “social acceptance”. Twee mogelijke, elkaar niet uitsluitende verklaringen werden voor deze observatie aangedragen. Ten eerste, uit onderzoek is gebleken dat men in Nederland de hoogste odds ratio kent om gepest te worden, wat zou kunnen verklaren dat meer Nederlandse kinderen met CP dan gebruikelijk zich gepest, gekweld en afgewezen voelen.

Ten tweede, kwalitatief onderzoek heeft laten zien dat kinderen met CP van tijd tot tijd graag op zich zelf willen zijn. Dit is in overeenstemming met onze PARS-III studie waarin we vonden dat kinderen met CP zich psychosociaal aanpassen aan hun motorische en bijkomende problemen door zich terug te trekken en hierdoor ook weinig vriendschappen ontwikkelen. Ouders / verzorgers maken zich zorgen over dit terugtrekgedrag en stoppen veel moeite in het creëren van mogelijkheden voor hun kind om sociaal betrokken te worden. Met andere woorden, het is zeer wel mogelijk dat de lage QoL scores op de domeinen “social support & peers” en “social acceptance” eerder te danken is aan de zorgen van de ouders / verzorgers dan aan ervaringen van kinderen zelf.

Wij concludeerden dat bovenstaande onderzoeksresultaten bijdragen aan een beter begrip van de QoL van Nederlandse kinderen met CP en dat deze informatie gebruikt kan worden om ouders en behandeld artsen te informeren. Verder kunnen hierdoor ook gezondheidsprogramma die beogen QoL in deze groep van kinderen te verbeteren, gericht worden op geïdentificeerd probleem domeinen.

DANKWOORD

DANKWOORD

Dit proefschrift is tot stand gekomen vanuit een gezamenlijke inspanning door een aantal mensen van zeer verschillende disciplines.

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DANKWOORD

Yvonne, jij introduceerde mij op het ganglab en bracht mij als eerste in contact met kinderen met CP. Jouw uitgebreide databasen zijn van onschatbare waarde geweest.

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Vles GF, Soudant DL, Honving MA, Vermeulen RJ, Bonouvrié LA, Vles JSH. Long-term follow-up on intrathecal Baclofen therapy in non-ambulant children with intractable spastic CP. 2012. In preparation.

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CURRICULUM VITAE

Georges (Joris) Vles werd op 11 november 1986 geboren te Maastricht. Na het voltooien van zijn VWO aan het Jeanne d'Arc College, startte hij met de opleiding geneeskunde aan de Universiteit van Maastricht. In de zomer tussen zijn eerste en tweede jaar werd hij door zijn vader, hoogleraar kinderneurologie, gevraagd om onderzoeksgegevens in te voeren. De interesse voor het doen van onderzoek was gewekt en 2 jaar later publiceerde hij zijn eerste artikel. Tijdens de rest van zijn studie geneeskunde bleef onderzoek een belangrijke nevenactiviteit en groeide uiteindelijk uit tot een promotietraject onder leiding van Professor Beuls en later Professor van Oostenbrugge. Het laatste jaar van zijn studie spendeerde hij aan orthopedische chirurgie in het Atrium Medisch Centrum onder leiding van Dr. Heyligers. Na het afronden van zijn studie vertrok hij naar Seattle, Washington, om daar onder leiding van Prof. Conrad een stage kinderorthopedie en orthopedische oncologie te doen. Dit werd gevolgd door een kortdurend traject als arts-onderzoeker bij de vakgroep neurologie van het Academisch Ziekenhuis Maastricht ter voltooiing van zijn proefschrift. Per 1 januari 2012 startte Georges als assistent op de intensive care in het Atrium Medisch Centrum, het ziekenhuis waar hij een half jaar later zijn opleiding tot orthopedisch chirurg zal beginnen.