Children and Young Adults in a Vegetative or Minimally Conscious State after Brain Injury

Diagnosis, Rehabilitation and Outcome

Henk Eilander

Adr. Heinen Uitgevers, 's-Hertogenbosch

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Kinderen en jong-volwassenen in een vegetatieve of laagbewuste toestand na hersenletsel

Diagnose, revalidatie en gevolgen

(met een samenvatting in het Nederlands)

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Hendrik Jan Eilander

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te Hengelo (O)

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Co-promotoren:	Dr. C.M. van Heugten Dr. P.L.M. de Kort

Voor alle patiënten én
hun familieleden

Contents

PREFACE

The story of Annelot and her father Frank

Case history

On December the 10th in 1997, Annelot got under a car. She was almost 16 years old. At arrival of the ambulance she was in a coma and showed a Glasgow Coma Scale (GCS)[3] score of E1M2V1, at arrival in the hospital the score was E1M4V1. She appeared to have a skull fracture in the left frontal region and an extracranial haematoma in the right tempo-parietal region. No other fractures were seen. She had to be ventilated. Annelot showed generalized epileptic seizures shortly after admission, and she suffered pneumonia. Two weeks later a herniation of the spine at level C5-C6 was diagnosed.
It is not clear when Annelot first opened her eyes. Four weeks after the accident, she opened her eyes when stimulated. She showed spontaneous eye movements in all directions, swallowed and moved her arms and legs, more on the left side compared to the right side. Occasionally, emotions were seen. She then was admitted to the rehabilitation centre Charlotte Oord[1], which provided a treatment programme for children and young adults in an unconscious state after severe brain injury (see at the end of this chapter).

At admission to EINP, Annelot appeared to be in a minimally conscious state[2]. She was very restless. Within a week, she started to talk, first with single words and soon with short sentences. Her short-term memory was disturbed and she needed much affirmation. In a period of two months, her physical functions as well as her cognitive functions recovered more and more, although she was quickly fatigued.

Nine weeks after the accident, Annelot started to get emotional about it. Furthermore, she appeared to be somewhat hyperactive in all sorts of activities and in her thoughts. She sometimes showed repetitive behaviour.

Twelve weeks after the accident, Annelot was able to participate in special education. First a couple of hours a day, but soon she went all weekdays. Her behaviour changed and she became a quite, helpful girl, although she sometimes also showed signs of depression. The more her capacities recovered, the less of these signs were seen.

Five months after the accident, Annelot was discharged from clinical rehabilitation. She still had therapies and special education. Two months later, she was fully discharged and her rehabilitation and education continued in more regular facilities nearby her hometown.
Now, more than ten years later, Annelot is a wonderful young woman, who enjoys life.

In this preface, Annelot and her father Frank share their stories.

[1] The Early Intensive Neurorehabilitation Programme (EINP) was developed in 1987 in the paediatric rehabilitation centre Charlotte Oord in Tilburg, the Netherlands, which merged into the rehabilitation centre Leijpark in January 1998.

Shocking moment

Frank
The company I worked for grew 20 % per year and in my new corporate position, I was responsible for the key accounts and the continued growth of the company. I had earned the respect of both the clients and the board of the company because of the continued growth.

I was on my way (as usual in December) to visit a customer to discuss the forthcoming year's business and prices. On this occasion, I had intended to stay overnight and Bernd (my customer and business colleague) had organised a hotel for me in the area. We would have dinner together with his staff, which I felt was important. Upon reaching my destination, I called my wife, Jacqueline, to tell her that I had arrived safely, a procedure I normally did as I spend about 40 to 50 nights per year away from home. "Are you driving?" my wife asked. I replied that I was. "Please pull over into the nearest lay-by", she said very calmly. What is this, I thought? There was a lay-by very close and I pulled into it.

My wife then began, "There are two policemen here at the door, telling me that Annelot had just had an accident. It is very serious. She is still alive, they think, but she is in a coma. We are going to the hospital now and I think you should come there too, as soon as possible. I know that you are more than 400 kilometres from home, but it is serious and we have all been asked by the doctors to come to the hospital."

Annelot
I was a teenager of 15 years old with a pretty stubborn and strong character. That day I went to my boyfriend's house for the first time. It was very pleasant and time past by quickly.
The same evening I had to baby-sit in our street. I had agreed with my mom that I would first come home to have dinner.
I was late and my boyfriend offered to ride home with me. He was on his scooter and I was with my bike.
At a busy crossing, we drove through the red light on the wrong side of the road, because this was faster. A car then hit me.

Others have told me about the accident, all I can remember are some images of that day. I can't remember anything about the moment the accident happened, which probably is the best.

Realising the situation

Frank
After a quick cup of coffee with Bernd, I was alone in the car with my thoughts and cried like a small child. Is she still alive? Oh Lord, please, please, please, let her live. And how will she come out, if she comes out? In a coma? What does this mean? Severe brain damage? What kind of future will she have? In a wheelchair, or in bed for the rest of her life? Will this be her future?
All these questions were going through my mind.
During the trip I received many calls from friends, family, my secretary, from my wife in the hospital (she still could not say whether Annelot would survive through the night), from my brother with great

sympathy and from others. Later I understood that this was just to keep me awake. The state police were advised by the police in our hometown to let me drive. The car number and situation was given countrywide to let me drive through so that I could get to the hospital as quickly as possible.
Finally at about 10 pm I arrived (it was like a horror-flight) at the ICU.
I did not recognize our daughter!
Was this real? Is this Annelot?

The evening was a mixture of emotions and was so unreal.
I could not stand up anymore, our oldest daughter decided to remain at her sister's bedside, and I was put into a small hospital bed and tried to catch a few hours of sleep. However, I could not sleep and needed to go back and join my daughter, so she could go to sleep and I could take over the watch by Annelots' bedside. I could not understand the whole situation. It was so unfair. Why Annelot? I really could not understand it.

Annelot

I don't remember the time when I was in a coma for 5 weeks. My friends told me about their visits in hospital and later on in Charlotte Oord. I wasn't aware of the situation…
My father told me that I was the first patient of the new clinic Leijpark. I can only remember vague moments like warm people around my bed and people who wanted something from me but I could not understand what. I only wanted to sleep. Please let me sleep.

Life goes on …. in another world

Frank

I started going to work again, part time, only walking and thinking. Life goes on, you think, and you try. Everybody encourages you, but all the time my thoughts were elsewhere. All those impressions: ICU sterile rooms, nurses, visitors, friends, and all those conversations I remembered in detail. I lived much more intense. I began to see many things from a different perspective and all the time the same question "why us, why Annelot?"
My wife Jacqueline visited Annelot every morning and I went to the rehabilitation centre every afternoon. Each weekend and evening, we visited her together with some friends and family.
My boss reacted in a negative way to all of this and I was no longer important to him. I was very disappointed and began to realise for the first time: "Is this the man that I worked for, the last 17 years?" I travelled throughout the whole of Europe for the company, stayed away from home for so many nights for the company, and missed many warm and private moments with my family. He never came to the hospital during this difficult period. He was

not there for me and was preoccupied with his business to make it even bigger. They say that in bad times you learn to understand who your real friends are and most of all, you learn the real importance in life. Your private life, your good health, your warm friends and the lots and lots of fun you had with them.

How to go on, making schemes for care at home, change my work, work from home? In this phase, I decided to change my working life and to stop working for this company any longer. Half a year later, I started with my own small company.

Annelot

Six weeks after the accident, the doctors declared me out of coma. Personally, I do not remember anything about this moment. The things they show on TV about coming out of a coma, like opening your eyes and remembering everything, did not take place in my case. On the contrary, little by little you wake up and learn to talk again, eat and walk again, think again. Your brain recovers very slowly.
It is as if you were born again and have to learn everything for the first time. Of course, this recovery is different for each person. I feel lucky that things turned out positive in my case, even with all the ups and downs. You start to realise the situation you are in and compare it with the situation before the accident. During this process, I had a lot of help from the psychologist in the revalidation centre. And from my family and friends who never stopped supporting me in many different ways. This was one of the main forces for me, along with my own perseverance, to deal with all the heavy and demanding therapies.

Therapy

Frank

Day by day, we saw Annelot improving slowly. We felt strong emotions with every small improvement. We remember things like her first movement with her feet. Did she move? Did you see that?
I can remember Jacqueline coming back home from another hospital visit and telling me in an apathic way that Annelot had opened an eye! "It was very short but I saw that she opened it just for a while", she said. However, the doctors in the hospital did not believe it. "It is probably a reflex", they said. We felt hopeless and not listened to. And from my car, I made a phone call to Charlotte Oord, asking to admit Annelot and to help her AND us. They agreed within a couple of days, and we received a warm welcome. Finally we met health professionals who were listening to us, with a lot of understanding, and accepting Annelot as a real person instead of a 'thing' that should be in bed. Therapies started immediately and slowly, bit-by-bit, we saw signs of improvement.
I just could not understand it from surprise, but a few days later, when I asked Annelot; "do you need anything else?" she said… "A KISS AND A SLEEP"
We started to communicate with our daughter again. Later on, I understood that this was more or less the moment she came out of coma according to the doctors. The many visits became a passion, we could hardly wait for the next visit, and we had better moments in Tilburg. Every day a step forward, although very small,

but forward. We started to live again and even with more enthusiasm. We captured these moments in our hearts, like hearing her first words, the first opening of her mouth and accepting the spoon with pudding, the goodnight kisses she started to give us when we left for home.
What I also do remember are the Pampers!! … Our daughter of 15 years had to learn everything again, as if she was born again and had arrived in another world. Her first three-wheel bike-tour in the central hall was another emotional moment for us, and the physiotherapist smiled from ear to ear.
Her first outdoor wheelchair ride was a big event and the sun started to shine again.

Annelot
After the accident, I was residential in treatment for 3 months in the rehabilitation centre. After that, I was semi-residential and went daily to the special education, adjacent to the rehabilitation centre.

During these months, a lot happened and I was very busy rehabilitating. I trained a lot during all the therapies and was always among people. I got a lot of attention from my family, friends and people from the centre.

I became aware of the situation for the first time, when I got home again, when I came back in the "normal" life and back into the community. In the rehabilitation centre, I was busy with myself and everybody helped me. However, back into the normal life, everybody is doing his own thing, nobody refers to the accident or the (invisible) handicaps you have.

New situation, ten years later

Frank
We now do talk about Annelot before and Annelot after. We understand that with her a miracle happened. She is the reason I got the guts to quit my job and start my own business. She was the reason I was able to see other things in life. She is the reason that we can enjoy every tiny moment in the family and that we have time for each other. She does not want to talk about it anymore and wants that people accept her the way she is now, but sometimes it is better to talk about it, as it would make her life easier. It would also help her to select friends who are more understanding and warmer. I need to accept that she is not choosing it this way. She has her own apartment now, her own friends, her own new life and her own job and salary. She is a "new born" person and I am very proud of being her father.

Preface

Annelot

I came across several new situations where they did not know my past, and I had to prove myself again and again. Personally, I do not want to talk about the accident with other people. I think it is important that people accept me for who I am, and not think about the "poor girl who was in an accident"

After the Mytylschool in Tilburg, I followed lessons in a special school in our neighbourhood.
Exactly one year after the accident, I got the terrific news I could go back to my old school where all my friends still were and where I had all the good memories. I followed this education on a lower level. Afterwards I attended secondary school (MBO) for 4 years and could study further in the 2nd year of higher vocational education (HBO).

My ambition was to reach the same level as before the accident. I succeeded! The next step is to get a job. I am now starting my second real job, with a trial period of two months. Until now, I worked temporary besides the study and the first job I tried, following my study was too heavy. I did not get the contract and in the review meeting, I was confronted with some 'little' remarks. Little to them, but huge to me.
The thought hit me again: "Should I talk about the accident in advance, or is it better to leave it out". My answer is still that they have to take me as I am. We will see.

My goals have been reached, with a detour, but I have come to the same level as before the accident. I had bad luck, but I also learned a lot from the accident. I am still growing and learning, but that is applicable for every 25 year old, I think! I fought hard and have beaten many misfortunes. Now I have my own apartment, a lot of good friends and a warm family around me. I now want to look at the future, try to fulfil my wishes and feel good about myself, and feel lucky!

August 2007

The Early Intensive Neurorehabilitation Programme

The story of Annelot and her father Frank is one of the many that could be told by over 200 patients who, since December 1987, were admitted to the Child Rehabilitation Centre Charlotte Oord or, after 1998, to the Rehabilitation Centre Leijpark, to take part in a custom-made treatment programme. The story reflects the clinical context in which this thesis has to be placed.

The Early Intensive Neurorehabilitation Programme (EINP) was developed in 1987 to meet the needs of an unconscious five-year-old girl, her parents, and the therapists who were involved in the treatment of the girl. The unexpected recovery of this girl to consciousness triggered a sequence of activities and events. This resulted eventually in the development of a unique special facility in the Netherlands, in which a treatment programme was executed aiming at the recovery of consciousness of young patients in a prolonged (at least 4 weeks) vegetative or minimally conscious state. The content of EINP is shortly described in Appendix 1. More information can be found on www.rcleijpark.nl.

The need for the evaluation of the programme in a systematic manner was expressed as early as 1989, but it was not before 1997 that the evaluation process actually was realised by developing a comprehensive research programme and by raising enough funds. It took three different phases in eight years until the project could be completed in December 2005, by publishing a scientific report[1]. This thesis is the result of parts of that research programme, focussing on the outcome in terms of level of consciousness, level of disability, quality of life, and long-term cognitive, emotional and social after-effects for patients and families. In a second thesis, recently Viona Wijnen reported about the neurophysiologic aspects that were studied in the research programme[4]. Together, in these two theses, the ultimate scientific justification of the research project is presented.

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CHAPTER 1

General Introduction

The presence of patients in a prolonged unconscious state is demanding for families, as well as for all professionals who are involved in the treatment and care of these patients[25,35]. Until recently, the general medical opinion about the possibilities of recovery of damaged brain tissue was that no newgrowth of nerve cells could occur, making the chances for good recovery very small. Nowadays we know that under certain conditions neurogenesis does occur, which may eventually result in better outcome than expected[39,46]. Still little is known about the specific conditions that are needed to enhance the neurogenesis. However, it has become clear that one way or another, doing exercises influences the process of neurogenesis and of the growth and pruning of axons, dendrites and synapses[7], resulting in better outcomes[50]. The question is whether these processes also emerge in patients in vegetative state or in minimally conscious state. And if so, questions arise whether treatments have positive effects and what the long-term functional outcome of these patients will be. Due to the practical, methodological and ethical difficulties in executing large, well-controlled clinical trials, research on the efficacy of treatments for severe disorders of consciousness is generally lacking[18,57].

In this thesis, three topics will be elaborated. Firstly, the focus will be on the concept of the different levels of consciousness, including the development of an observation scale: the Post-Acute Level of Consciousness scale (PALOC-s). Secondly, the outcome in terms of level of consciousness of the patients who participated in the Early Intensive Neurorehabilitation programme (EINP, as shortly discussed in the Preface) will be described. An attempt will be made to investigate the efficacy of EINP. Thirdly, the long-term outcome, social participation and quality of life of the patients, and the involvement and used coping strategies of family members will be described.

In this chapter the theoretical background of all major themes involving young patients in an unconscious state are elaborated, resulting in the expression of the research questions to be answered.

Epidemiology of severe brain injury

Severe brain injury is usually defined by depth of the coma as measured with the Glasgow Coma Scale (GCS)[52], combined with the duration of the comatose state, although a lack of uniformity can be seen in the international literature[35]. Patients with a GCS-score of 8 or less, who stay in a comatose state for at least 6 hours, are considered to be severely brain-injured. Many of them suffer from secondary injuries, in the brain as well as in other organs.

Traumatic brain injury is the most common cause of severe brain injury. Especially persons between 15 and 26 years of age are at risk because of dangerous traffic behaviour, although all kinds of traffic legislation diminished the percentages the last decades[35]. Almost twice as much males than females suffer

from a traumatic brain injury. In young children up to five years of age, non-accidental events like encephalitis or near-drowning are the most common causes of severe brain injury[5].
The incidence of children who suffer severe brain injury is estimated between 10 and 30/100.000, resulting in the Netherlands yearly in about 330-1000 new patients with severe brain injury[29]. How many of these patients still are unconscious one month after injury is unknown. Whenever a special rehabilitation programme for patients in a prolonged unconscious state should be provided, the number of patients who should be admitted has to be known.

Levels of (un-)consciousness

Coma is the state of loss of consciousness immediately after a brain involving incident, in which the patient is not arousable and lies with the eyes closed[44]. Patients neither speak understandable words, nor make any directed movements. On noxious stimuli at best reflexes can be observed. The cause of coma lies in the dysfunction of the ascending reticular activation system of the brainstem[44] which can be originated by many different processes in all parts of the brain.
Patients who remain in coma for a longer period (several days) generally end up in a vegetative state within one month. The concept of the Vegetative State (VS) was proposed in 1972 by Jennett and Plum[26], to distinguish it from coma, because of the long-term implications. Despite the presence of wakeful periods, the patients show no evidence of awareness of the self or the environment whatsoever, and there is absence of any purposeful responses to stimuli or to questions. Generally, patients in VS show adequate maintenance of respiration and circulation[18,47].
Almost 25 years after the introduction, it was recognized that the description of the VS is not suitable to some of the patients, who lack full consciousness and are not able to communicate, but who do show signs of purposeful behaviour, sometimes even in reaction to simple questions or commands. In 1996 the International Working Party on the Management of the VS (IWP) published a report in which the Low Awareness State (LAS) was proposed[2], followed a year later by the presentation of the Minimally Conscious State (MCS) by the Aspen Workgroup on the Vegetative and Minimally Conscious States[20]. Since then, the latter concept is accepted internationally. In both publications, the descriptions were generally clinical based, without extensive theoretical considerations. From that clinical point of view, the IWP distinguished some sublevels within the VS and the MCS, as well as a sublevel in between both states[2].The Aspen group opposed the distinction of sublevels within the MCS[20]. Both groups indicated the difficulties in distinguishing VS from MCS and MCS form full consciousness in patients who are on the border of two states.
There is no single quantitative or qualitative dimension that defines recovery of consciousness. So there is an urgent need for diagnostic instruments that can help to define the level of consciousness.

Assessment of consciousness

The assessment of persons with long lasting disturbed consciousness bears some pitfalls, easily resulting in misdiagnosis. Andrews et al. found a rate of 43% of patients who were diagnosed as in a vegetative state, but were actually (minimally) conscious[3]. Physical and visual disorders prevented the patients from reacting purposeful. Recently Schnakers et al. showed that this may still occur, despite the use of more sophisticated observation scales[48].
At least two main problems can be identified which can be responsible for misdiagnosis. Firstly, the condition of a prolonged loss of consciousness is rather rare and patients are dispersed to many possible health institutions around the country, resulting in a lack of experience of the staff that is responsible for the assessment[30]. Secondly, there is no single instrument that has been proven reliable and valid in assessing possible different levels of consciousness[18]. The Glasgow Coma Scale[52] is developed to monitor the depth of the coma during the acute recovery period in the first hours or days postinjury, but is not suitable in the post-acute stage in which vegetative or minimally conscious patients show spontaneous eye-opening. In the last 20 years, a range of observational scales[8,28,42,43] have been developed to measure possible changes in the behaviour of unconscious patients, often without thorough psychometric analysis[18]. As mentioned earlier, after the introduction of the distinction between the vegetative state and the minimally conscious state, even with some possible sublevels, the need for a single reliable and valid assessment tool is high. Subsequently, according to Lavrijsen et al., the investigation of the level of consciousness should always be executed by experienced staff, in a multidisciplinary approach, in cooperation with the patients' family[31].

Prognosis of recovery

In 1994, the 'Multi-Society Task Force on the Persistent Vegetative State' (MSTF) published a consensus statement, "summarizing the actual knowledge of the medical aspects of the persistent vegetative state in adults and children" ([37], pp 1499), including a prognosis for recovery[38]. The presented figures were based on earlier research: five studies of traumatic brain injured children (the oldest out of 1981), totalling106 patients, and three studies of non-traumatic brain injured children, totalling only 45 patients. The criteria for including the studies, or the used method to transform the research data into the outcome categories as used by the MSTF were not given. These publications of the MSTF still are the standard of knowledge, since no comparable studies are published since then. Although the MSTF calculated the *probability* of recovery, including the 99% confidence interval, in later articles referring to the figures of the MSTF, the uncertainty margins usually are not given[4,24].

Recovery can be characterized along two dimensions: recovery of consciousness and recovery of function. The chances to become conscious again after being in VS

for at least one month are, according to the MSTF, reasonable for children with TBI: 62% had regained consciousness at 12 months. For children with non-TBI, the chances are small: only 13% had regained consciousness at 12 months after injury[38]. In both groups, however, more than half of the patients who recovered to consciousness remained severely disabled. It can be questioned whether these figures are still valid: in the meantime the care at the ICU's has changed according to new insights, and the application of early rehabilitation programmes may influence the rate and amount of recovery.

Long-term consequences

Generally it is clear that severe brain injury unequivocally leads to long-term disturbances in one or more functional capacities[33]. Psychological functions like attention, memory, executive functions, metacognition, and social behaviour are most likely to be disturbed, and are of importance in social adaptation[15,21]. The distribution of problems is highly variable, depending on the site and extent of damage. In some patients the disabilities are subtle and easily being ignored without proper neuropsychological testing[23]. Although the figures are sometimes controversial, it seems that young children with severe brain injury ultimately have less favourable outcomes[1].
Most of the patients who suffered severe brain injury will remain at least partially disabled in the long-term. In a population study, Hawley et al. concluded, at a follow up between 1 and 6 years after injury, that 69% of children, aged 5-15 years at injury, were moderately disabled and 8% were severely disabled[22]. They did not report of any child still in a vegetative state at follow up. Of 69% of the children with severe brain injury, the personality had changed, according to their parents. Only 37% of the severe brain injured children received any form of therapy following the injury. Whether recovery of function can be enhanced by providing intensive rehabilitation in an early phase is not known yet.

Not only the functional level, but also the perceived quality of life is of importance in establishing long-term consequences of severe traumatic brain injury[10,13]. Initial results show surprisingly that patients with mild brain injury are more negative about their quality of life, compared to severe brain injured patients[9]. It is possible that the latter group lacks insight in their own situation, but it also may be that their situation is better adapted to their disabilities. Nevertheless, it seems important to incorporate the patients' perspective in outcome research.

Family involvement

Having severe brain injury is not only a patients' problem, but is as much a family matter, as Williams and Kay argued already in 1991[60]. Many family members suffer prom post-traumatic stress, resulting in behavioural and personality disorders, without proper identification or treatment[40]. Nevertheless, in most cases family members are highly involved in caring for the brain injured patient during recovery. This is especially the case in

young patients. Ylvisaker & Feeney pleaded some years ago to incorporate family members actively into the rehabilitation process[61]. Initial results show clear evidence of the efficacy of this approach in diminishing the effects of the brain injury on themselves[54] or on the injured child[16,17].
Therefore, every outcome study of a treatment programme should not only incorporate patients, but also proxies, focussing on their capabilities to cope with the situation and the effects on the level of functioning of the patients.

Treatment programmes

Before recovery of functions can be pursued, recovery of consciousness should occur. The question, what processes are needed to establish recovery of consciousness cannot be answered easily. The nowadays assumed plasticity of the brain in neurologically impaired patients[45] reinforces the importance of a proper and early treatment. Generally, it is thought that sensory stimulation can contribute to recovery of consciousness, and there is some evidence that sensory deprivation results in physical deterioration of the brain[14]. All over the world comprehensive treatment programmes are developed, sometimes with promising outcome results[41]. Yet, the complexity of executing research makes it difficult to demonstrate the effectiveness of comprehensive treatment programmes in severe brain injured patients[57]. A Cochrane systematic review revealed that there is no reliable evidence to support or rule out the effectiveness of sensory stimulation programmes in order to regain consciousness in unconscious patients[34]. Nevertheless, it is inevitable and necessary that clinicians, in the absence of clear-cut guidelines, develop a systematic approach to the assessment and treatment of severe brain injured patients[19]. The earlier after the injury this approach is executed, the better the outcome[14], as is also the case when the intensity of treatment is increased[49]. Every rehabilitation facility that admits severe brain injured patients, even in an unconscious state, faces the challenges to develop its own strategy in handling these patients, bearing in mind the above mentioned research results and limitations. In the Preface we described such a process, resulting in the development of EINP.

Theoretical base of the Early Intensive Neurorehabilitation Programme

Recently Whyte called upon using treatment theories as a base for designing effectiveness studies in brain injury rehabilitation[58]. In the research project of which this thesis reports, such treatment theories are formulated. The underlying theories of the Early Intensive Neurorehabilitation Programme (EINP) can be summed up by three basic principles. Firstly, the plasticity of the brain is an important biological phenomenon, which is of great adaptive significance in healthy brains as well as in injured ones[11,53,55]. Secondly, recovery processes start early, from the moment of injury, and can last long, even many years, based on a range of different neural mechanisms[6,7,51].

And thirdly, the brain appears to be highly sensitive to external and internal sensations and responds to it by rewiring, changing of (sensory) representations, reorganization[27], and newgrowth of neurons, dendrites and axons in order to adapt in the best way possible to what is needed[6,36].
Inevitably, the effectiveness of these principles have to be investigated in clinical based research.

Research designs in evaluating brain injury rehabilitation

Almost every article on the treatment of severe brain injured patients stresses the difficulties facing executing proper research, in which many obstacles can be identified[14,57].
Firstly, there is a problem of the possible group size. In brain injury the characteristics of the patients are diverse: the cause of the injury, the effects on the brain tissue, and possible co-morbidity can vary considerably. In addition, it is not possible to investigate all important features, for instance the presence of micro lesions. Moreover, one has to ask which factors are important in relation to the outcome measure. For instance, the level of education is of importance in examining the return to work, but not in examining the ability to walk. Therefore, many variables should be taken into consideration, sometimes making it impossible to form subgroups of substantial size. Furthermore, it can be doubted whether the incidence of patients in a vegetative or minimally state is high enough for creating group studies. Recently, Lavrijsen found just 32 patients of all ages being in a vegetative state in one of the 380 Dutch nursing homes and long-term nursing care facilities[32].
Secondly, when treatments are to be compared, it can be difficult to define the precise content. Treatments that are called the same name can differ substantially between various rehabilitation facilities in small but important details as well as in the gross lay-out. Also, most rehabilitation treatments are multifaceted and interactive. Identifying the hypothesized active ingredients in complex rehabilitation programmes is almost impossible, and comparing two or more programmes is only possible in global terms[56].
Thirdly, there is a problem of measurements. The methods to measure outcome can be questioned. It is of great importance that the used measures are valid and reliable. Besides, it depends on the phase patients are in, what outcome measures are of importance. In the acute phase, survival is probably much more important than in the chronic phase, in which the level of independency and the quality of life are important outcome measures.
Probably the most important problem in executing proper research, however, is one of ethics, especially when children are involved. The issue of the vegetative state brings about many emotions[25]. Especially the moments of choice (to treat or not to treat; where should treatments take place) often cause stress within and between people[12]. It can be assumed that parents are to much stressed and will refuse to cooperate in a randomized controlled trial when they should take the risk that their

child will not take part in the treatment branch.

Considering all of these problems, to be able to evaluate EINP, the choice had to be made to develop a comprehensive research programme consisting of different parts, in order to have the best chances to draw any conclusions. The first option was to execute a control group study, but also observational cohort studies, neurophysiologic studies and long-term outcome studies were developed and executed.
About the neurophysiological results, a separate thesis has been written[59].

Objectives of the thesis

The initial and main objective of this thesis was to evaluate the efficacy of EINP.
An attempt has been made to identify a control group, for comparing the long-term functional outcome between the two groups, generating also figures about the incidence of young patients in a vegetative or minimally conscious state after severe brain injury in the Netherlands. Because the incidence of TBI, however, appeared far below expectation and the majority of the patients all over the Netherlands had been admitted to EINP, it appeared to be impossible to create such a case-controlled group.
Furthermore, the outcome was studied by describing the course of the Level of Consciousness (LOC) of the admitted patients. To be able measuring the LOC, an observational instrument had to be developed. Moreover, the long-term outcome of the admitted patients in terms of level of consciousness, level of disability and experienced quality of life were evaluated. And finally, the perspective of close relatives on the patients' quality of life and the ways of coping by these relatives was investigated.

Outline of this thesis

Firstly, in Chapter 2, the development of the Post-Acute Level Of Consciousness scale (PALOC-s) will be described, in which the reliability, validity, and responsiveness were investigated.
In Chapter 3, the attempt to identify a control group of patients who were not admitted to EINP will be described. A survey was executed in all Dutch major hospitals with neurosurgery intensive care units (ICU's), offering also the possibility to investigate the incidence of young patients in a VS or MCS, one month after suffering traumatic brain injury.
In Chapters 4 and 5, the focus will be on the development of the level of consciousness of all patients, who were admitted to EINP. Chapter 4 addresses the retrospective analysis of the medical files of 145 patients, while Chapter 5 describes the prospective investigation by repeated measurements of the level of consciousness of 44 patients. In these chapters, also the question will be answered, whether it is possible to predict the recovery of patients by any relevant variable, like the type of injury, age, time between injury and admission, and the level of consciousness at discharge form hospital.
In Chapter 6, the long-term functional outcome of a part of the retrospective

cohort will be described, comparing TBI with non-TBI patients. Moreover, the issue what outcome scale presents the best information in long-term outcome research of severely brain-injured patients will be addressed.
In Chapter 7, the focus will be on the long-term quality of life and presence of depressive symptoms of the patients who recovered to consciousness, as well as on the coping capabilities of relatives. In addition, the possible relation between these phenomena is explored.
Finally, in Chapter 8, conclusions will be drawn concerning the efficacy and usefulness of EINP and about the usefulness of the PALOC-s, methodological issues will be discussed and recommendations will be formulated.

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CHAPTER 2

The reliability and validity of the PALOC-s: A post-acute level of consciousness scale for assessment of young patients with prolonged disturbed consciousness after brain injury

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Abstract

Objective
Validation of the Post-Acute Level Of Consciousness scale (PALOC-s) for use in assessing levels of consciousness of severe brain injured patients in a vegetative state or in a minimally conscious state.

Subjects
A cohort of forty-four successively admitted patients (between 2 and 25 years of age), who were treated in an early intensive neurorehabilitation programme, were included in this study.
Methods and procedures
Each patient was examined, using the Western Neuro Sensory Stimulation Profile (WNSSP) and the Disability Rating Scale (DRS), once every two weeks resulting in 327 examinations (all videotaped). To determine the reliability of the PALOC-s, six observers rated one videotape of each patient. One of the observers rated the same tapes a second time, 3 to 4 months later.
The validity was determined by correlating 100 ratings of one observer with the scores on the WNSSP and the DRS.
To determine the responsiveness of the PALOC-s, the size of change between the scores of the first and last examinations were calculated.

Results
The inter-observer correlations and agreement scores varied between 0.82 and 0.95. The intra-observer correlation and agreement scores varied between 0.94 and 0.96.
The correlations with the WNSSP varied between 0.88 and 0.93, and with the DRS, the correlations varied between 0.75 and 0.88.
The responsiveness was significantly high (t=8.2), with a standardized effect size of 1.30.

Conclusion
The PALOC-s is a reliable, valid, and responsive observation instrument provided it is administered after a structured assessment by an experienced and trained clinician. The PALOC-s is feasible for use in clinical management, as well as in outcome research.

Key words
Level of consciousness
minimally conscious state
reliability
responsiveness
severe brain injury
validity
vegetative state

Introduction

Severe brain injury as defined by a score of eight or less on the Glasgow Coma Scale (GCS)[60] is generally characterized by a prolonged loss of consciousness, defined as coma, a state in which the eyes of the patient are closed. The mere opening of the eyes does not necessarily signify the return of consciousness. This unconscious state, according to the initial description of Jennett and Plum[38], is generally called the Vegetative State (VS).
Ever since its introduction, the term 'vegetative state' has given rise to discussions. These discussions concern the name of the syndrome, the nature, the probable duration, the treatment that should or should not be given, the existence of a possible variant for children and so on[2,11,18,27,40,55,56]. One of the most discussed topics concerns the variability of the observed symptoms[3]. Some patients are completely motionless, while others can make all kinds of automatic movements. Some patients show emotions, often in reaction to stimuli, while others show no reaction at all. The introduction of the concepts of the Minimally Responsive State (MRS) by the American Congress of Rehabilitation Medicine[2], the Low Awareness State (LAS) by the International Working Party on the Vegetative State[4] and the Minimally Conscious State (MCS) by the Aspen Neurobehavioural Conference[28], offered (new) possibilities to describe unconsciousness from coma to full consciousness including all levels in-between. The key feature of all three concepts is the introduction of a level of consciousness that is neither comatose or vegetative nor fully conscious. The introduction of such a state makes it easier to monitor the course of recovery from coma to full consciousness.
Patients with severe brain injury do not recover suddenly from the comatose or vegetative state into full consciousness. When they show any signs of recovery, one can see a broad range of slight behavioural changes, diverse and inconsistent awareness of themselves or their surroundings, increasing reactivity and cognitive understanding. It is obvious that the different patient capabilities require different treatments[4,45,61].
Recently, the need for accurate differential diagnosis has been identified as the essential first step in clinical management of patients with consciousness disorders[24].
In the last three decades, different techniques and scales have been developed to monitor the possible recovery in the level of consciousness of patients[6,9,16,26,29,34,37,52,53,58]. Some of these scales are not very sensitive to slight changes in responsiveness of vegetative or minimally conscious patients. Others are aimed at monitoring the depth of the loss of consciousness in the acute phase, such as the Glasgow Coma Scale (GCS)[60], or have been designed to measure gradual changes in the level of cognitive recovery of patients who are in a diminished state of consciousness, such as the Western Neuro Sensory Stimulation Profile (WNSSP)[6]. The Rancho Los Amigos Levels of Cognitive Functioning (RLA)[34], which is commonly used in evaluating rehabilitation of patients with traumatic brain injury, focuses on cognitive and behavioural recovery. Some scales focus on reactions to specific sensory stimuli,

such as the Sensory Modality Assessment Rehabilitation Technique (SMART)[29] and the Sensory Stimulation Assessment Measure[52], while other methods rely on qualitatively described behavioural aspects, such as the Wessex Head Injury Matrix (WHIM)[58].
However, none of these scales were developed to distinguish between the VS and the MCS, including the possible sublevels within these two states.
In order to evaluate the effect of a treatment programme aimed at the recovery of consciousness[15], an observation scale measuring the levels of consciousness more precisely was needed. This resulted in the development of the Post-Acute Level of Consciousness scale, the PALOC-s. The observation scale consists of eight different (sub)levels of consciousness, from coma through vegetative and minimally conscious states to full consciousness (see Appendix 2). If the PALOC-s appears to be a reliable and valid instrument, its applicability can possibly be extended to the work of others aimed at developing and evaluating treatment programmes for unconscious patients.

In this study, the reliability, validity, and responsiveness of the PALOC-s were investigated in a cohort of children, adolescents, and young adults. Firstly, the reliability and the responsiveness of a draft version of the PALOC-s were determined and secondly for the reliability and validity of the final version were determined.

Methods

Participants
All 44 patients who participated were admitted to an early intensive neurorehabilitation programme (EINP) in the Rehabilitation Centre Leijpark in Tilburg, the Netherlands, between January 2001 and September 2003. Admission criteria for EINP were: severe brain injury (initial GCS at time of injury ≤ 8), between 2 and 25 years of age, in VS or MCS, independent of life support systems such as artificial respiration, and admission within six months after a traumatic or a vascular injury, or within three months after an anoxic injury. No patients above the age of 25 were admitted, due to the origin of EINP in a rehabilitation centre for children.

Outcome measures
PALOC-s
The PALOC-s was developed in 1998, based on the publications of the International Working Party on the Vegetative State[3,4], and of the Aspen Neurobehavioural Conference[28]. In the PALOC-s, eight hierarchal levels were distinguished: Coma (1), VS hypo-responsive (2), VS reflexive state (3), VS high (re-)active (4), MCS transitional state (5), MCS inconsistent reactions (6), MCS consistent reactions (7), and Consciousness (8). Each level was illustrated with three to four short descriptive sentences. Because the level of arousal and awareness of unconscious patients can alter in a time span of minutes[5,64], three states are discerned in scoring the PALOC-s: the 'general state', the 'best state', and the 'worst state'.

The complete PALOC-s is presented in Appendix 2.

WNSSP

The protocol from the Western Neuro Sensory Stimulation Profile (WNSSP) was used to examine patients[6] in a systematic manner. The WNSSP was developed to assess slow-to-recover patients with severe brain injury, and can be used for clinical evaluation as well as for the study of recovery patterns. The WNSSP consists of 33 items, representing a broad range of behaviours: arousal and attention, expressive communication, and the responses to auditory, visual, tactile and olfactory stimulation. The WNSSP results in a total score varying between 0 and 113, indicating the level of alertness, the level of cognitive functioning, and the appropriateness of reactions on simple commands.

In a small pilot study conducted in 1996 with seven patients, it was found that this protocol has good qualities for repeated structured examinations of young unconscious patients function levels[14]. Therefore, despite a mild floor effect which was shown to be present in this instrument[47], it was decided to use the WNSSP-protocol for this study. Recently, Lavrijsen et al. proposed to use the WNSSP protocol in order to differentiate vegetative patients from patients in coma, in a locked-in state, or in a minimally conscious state[40].

DRS

The Disability Rating Scale (DRS) was used to establish a global level of disability. The DRS has been developed for quantitatively assessing the disability of patients with severe brain injury[55], the outcome ranging from coma to independent participation in the community. The DRS consists of eight items and results in a score from 0 (no disability) to 29 (extremely vegetative). A score of 30 is used in outcome research when a patient has died. The DRS has been recommended as one of the most appropriate instruments in assessing the (long-term) outcome of severely brain injured patients[11]. The first three items of the DRS are very similar to the items in the GCS, assessing arousal, reactivity and responding. The next three items assess the level of cognitive independency during self-care activities. The last two items measure the level of community participation.

Patient assessment

Patients in this study were examined once every two weeks from admission to discharge by the first author, who is a neuropsychologist with more than 20 years experience regarding rehabilitation of brain-injured children and adolescents. In a small quiet room, the patients were seated in a wheelchair or in an upright position in bed. The examination began with a three-minute period without any stimulation followed by the application of the WNSSP. After concluding the WNSSP, another three-minute silent period was established. The total procedure lasted between 15 and 30 minutes. Immediately after this examination the investigator calculated the WNSSP scores, administered the PALOC-s, and part of the DRS (items 1,2,3,7, and 8). During the same day, the last part of the DRS was administered (items 4,5, and 6) after consulting the nursing staff.

The total examination procedure was recorded with a Hi8 video camera. The camera was placed at a height of two meters in front of the chair or bed. In most of the cases, the patients were captured fully on film. Sometimes the lower parts of their legs, and/or their feet were out of range of the camera. It was not possible to zoom in on the patient. Therefore, small movements of the eyes and face could not always be detected.
Some items of the WNSSP could not be administered in all cases. For instance, young children were not able to read simple commands and patients without a pupillary reflex could not be stimulated by shining a bright light into their eyes. In those cases, the items were skipped and the scoring was adapted, as explained in the statistical analysis paragraph.

Validation procedure

Development and initial validation of the PALOC-s
To examine the usefulness and reliability of the first draft of the PALOC-s, four observers were recruited: three physicians and one neuropsychology trainee, all with relevant experience in examining neurologically severely impaired patients. Participation of the observers was voluntary. They were trained by having them study the relevant literature[3,4,21-23], and by having them attend two training meetings, together with the first author. During the meetings the objectives and the design of the study were explained, the PALOC-s was discussed and five videotapes of the examination of patients were observed and discussed, resulting in scoring the PALOC-s. The videotapes used in this training procedure were excluded from the actual study. Of the remaining videotapes, one tape of each patient (n=44) was selected. Half of the tapes were selected at random and half of them were chosen in such a way that in each category of the PALOC-s at least three tapes were present, according to the rating score of the examination by the first author,. Each tape was copied on to a VHS-tape and randomly numbered to avoid any possibility of identification of the patient. In a period of two to three weeks, each observer rated 11 tapes in a unique, randomly determined sequence. After each period, the sets were exchanged, until all tapes had been observed by each of the 4 observers. In this way, the inter-observer reliability could be determined
To determine the test-retest reliability, one observer (the neuropsychology trainee) rated the same 44 tapes again in a new random sequence, four to six months later. During a discussion round at the end of this procedure, the usefulness of the PALOC-s was discussed. The four observers proposed changing some unclear descriptions of the three minimally conscious levels and of the conscious level. These changes were discussed with the clinical treatment team of EINP, who had become very experienced using the PALOC-s. Finally, the proposed version was discussed in writing and via e-mail with the four observers. The first author then made the final decisions regarding the formulation of the PALOC-s items. The final version of the PALOC-s is presented in Appendix 2, while examples of the changes that were made with regard to the first version are presented in the Appendix at the end of this chapter.

Reliability of the final version of the PALOC-s
To investigate the reliability of the final version of the PALOC-s, two more observers were recruited: a psychology trainee without clinical experience and a general practitioner who was a member of the clinical team in 2006. They were trained according to the above-described procedure, seeing the same five videotapes as the first four observers did. Subsequently, and unaware of the ratings of the first four observers, they observed and rated the same 44 videotapes, each in a new random sequence.

Responsiveness
The responsiveness of a scale is the sensitivity of that scale to measure changes over time in the observed variable. To determine the responsiveness of the PALOC-s, the investigator's scores of the assessments during admission and discharge were compared.

Validity
To investigate the validity of the PALOC-s, 56 more videotapes were randomly selected out of the remaining 278 and, together with the original 44 tapes, observed in a random sequence by the psychology trainee without clinical experience. This resulted in 100 ratings. Subsequently, these scores were correlated to the scores of the WNSSP and DRS to determine the concurrent validity.
Some patients were represented two to four times in this total of 100 tapes. To analyse the effect of the multiple representations of the same patients on the validity scores, all ratings were divided into four subgroups, in such a way that each patient was represented only once in each subgroup. The first subgroup of scores consisted of the ratings of 44 patients based on the original tapes, the second subgroup consisted of ratings of 36 new tapes of these 44 patients, the third of 16 other tapes of the 44 patients, and the last subgroup of scores consisted of ratings of 4 more tapes of the 44 patients.

Statistical analyses

The raw scores of the WNSSP were firstly converted into percentages first (WNSSP%), based on the highest attainable score of all the items that were actually administered. This was done because in some cases not all items could be administered (see patient assessment).
The inter-observer reliability scores and the intra-observer test-retest scores were calculated by using Spearman's rank-order correlation coefficient (r_s).
The inter-observer agreement scores and the test-retest agreement scores were calculated by using Cohen's weighted Kappa (κ_w).
The responsiveness is defined as the ability of the PALOC-s to detect changes in the clinical state of the patients during the course of admission to EINP, comparing the scores of the first and last examination by the first author. The responsiveness was investigated by calculating the standardized effect size according to Cohen, that is by dividing the mean difference between the first and last examination scores by the mean of the standard deviations of the first and last examination scores (0.2 is a small effect, 0.5 a moderate affect and 0.8 or higher represents a large effect). In addition, the

paired t-test was used to investigate the significance of the changes.
To investigate the validity of the PALOC-s, Spearman's rank-order correlation coefficient (r_s) was used, correlating the PALOC-s with the WNSSP% and the DRS. Spearman's rank-order correlation coefficient (r_s), mean scores, standard deviations and the t-test score were calculated using SPSS version 11.0.1. Cohen's weighted Kappa (κ_w) was calculated using MedCalc version 7.3.0.1. To control a possible age effect on the scores, the total group was split into three age groups: 2-10 years (N=11), 11-20 years (N=22), and older than 20 years (N=11) In each subgroup the above mentioned Spearman's rank-order correlation coefficients (r_s) were calculated.

Results

Patients' characteristics
A cohort of 44 consecutively admitted patients (aged 2-25 years, mean (M)=16.0; 64% male; 73% traumatic) with severe brain injury (initial GCS at time of injury ≤ 8) participated in this study. Admission to EINP took place between 23 and 198 days after injury (M=71, SD=25.5), between January 2001 and September 2003. All patients were in a vegetative state (77%) or in a minimally conscious state (23%) upon admission. This was determined by the clinical team, using the classification presented in 1996 by the International Working Party on the Management of the Vegetative State[3,4], with one exception. In order to avoid uncertainty, the clinical team decided to classify the 'transitional state' as MCS instead of an undecided category between VS and MCS.
As the length of stay varied between 26 and 197 days (M=111, SD = 41.1), and sometimes patients could not be examined because of their physical condition, the number of examinations per patient varied in accordance (range 2-14). This resulted in a total number of 327 videotaped examinations.
To demonstrate the clinical applicability of the PALOC-s, three cases out of the 44 are presented throughout this paper in Boxes 1, 2 and 3.

Box 1.

Clinical presentation and acute management

Patient 1 is a boy, who was 17 years old at the time of his injury. He was injured after joyriding under the influence of alcohol and hitting a bridge. He was found unconscious at the scene of the accident, where his GCS score was E1M4V2.

Initial CT brain scanning demonstrated hypoxia, punctual haemorrhages, diffuse axonal injury, and a contusion to the brain stem. Some large haemorrhages were shown in the left parietal, right frontal and temporal lobes. There was also an impression fracture left parietal. The bone fragments were removed surgically. There were fractures to the jaw, the right mastoid, a perforation to the left ear, and an epidural haematoma. Patient 1 spent 20 days in the ICU. As small amount of progress was observed: he opened his eyes to stimulation now and then, however there were no verbal responses. His GCS score progressed to E3M4V1. He was ultimately transferred to EINP 39 days after his injury.

Rehabilitation programme and progress

At admission patient 1 was in a vegetative state (PALOC-s level 2, see Figure 1) and showed little muscle tension. He was undernourished, showing only substantial reactions to pain during passive movement of his shoulders. When his level of consciousness gradually improved, he appeared to become fatigued very quickly, demonstrating this as a staring gaze. He was not able to fixate on pictures or objects. Within weeks he was able to make eye contact for a couple of seconds. His motor responses improved. His facial mimic developed more and more, and sometimes he made sounds. He gradually started to smile and to look angry at people (PALOC-s level 5). He was capable of showing whether he liked something or not. There were periods in which he shut his eyes to isolate himself from his surroundings.

During the following recovery process, patient 1 showed resistance to the presented activities. He looked very angry; making threatening gestures, pushing away material, and isolating himself by putting his hands in front of his face. His mimic and behaviour could vary within situations. It was not clear whether these changes expressed his real emotional intentions. Patient 1 slowly became more cooperative and more directed towards tasks (PALOC-s 6). However, his attitude shifted and he became more and more resistant towards any activity. Patient 1 appeared depressed, for which medication was administered. His mood improved within several days, however, there was still tendency to act clownish, which made him difficult to handle.

At 195 days after admission to EINP, patient 1 was discharged to a regular rehabilitation facility. The PALOC-s score at discharge was 7 and the DRS-score was 9; 3.4 years after discharge, the DRS-score was 7.

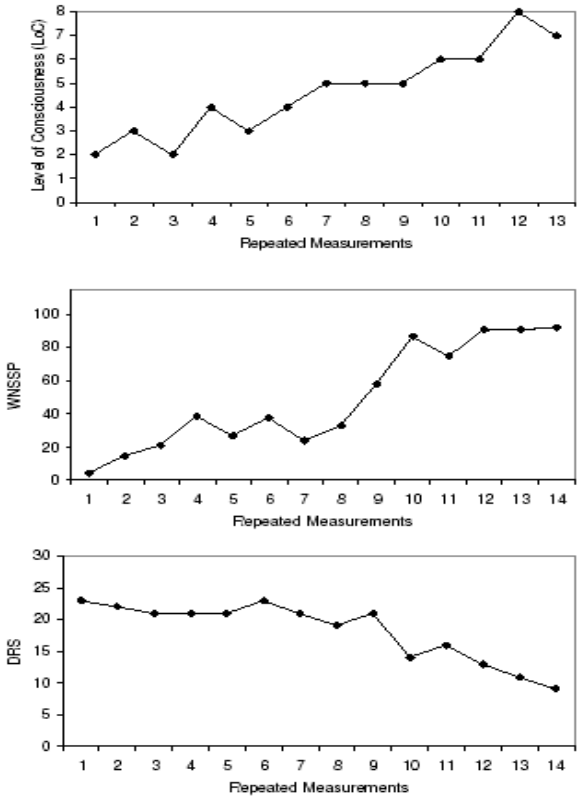

Figure 1. Graphic presentations of the PALOC-s, WNSSP and DRS scores

Development and initial validation of the PALOC-s

The multi-rater inter-observer reliability of the PALOC-s draft version is presented in Tables 1 and 2. The correlations varied between 0.85 and 0.94 (Table 1), and the kappa's varied between 0.85 and 0.95 (Table 2), while the Standard Error (SE) was small in all cases.

The test-retest reliability correlation was 0.96 for the 'general state', 0.95 for the 'best state' and 0.96 for the 'worst state'. All these correlations were significant at the .01 alpha level.

The test-retest agreement kappa was 0.94 for the 'general state', 0.94 for the 'best state', and 0.95 for the 'worst state' (SE in all cases = .02).

Table 1. Correlations (r_s) between the six pairs of observers on the draft version of the PALOC-s

Pairs of observers	r_s general	r_s best	r_s worst
1 x 2	0.94**	0.86**	0.92**
1 x 3	0.92**	0.90**	0.94**
1 x 4	0.85**	0.85**	0.89**
2 x 3	0.94**	0.92**	0.92**
2 x 4	0.92**	0.92**	0.94**
3 x 4	0.92**	0.88**	0.91**

** p < .01 (2-tailed)

Responsiveness

The change score on the PALOC-s between the first and the last examination during admittance to EINP was positive (indicating improvement), with a t-test score for paired samples being 8.24 ($p<0.01$).
The standardized effect size according to Cohen was 1.30, which can be considered as high.

Reliability

For the final version of the PALOC-s, the two-rater correlation score for the 'general state' was 0.94. The correlation for the 'best state' was 0.88 and 0.94 for the 'worst state'. All these correlations were significant at the .01 alpha level. The two-rater agreement kappa score between the fifth and sixth observer was 0.94 (SE=0.02). The kappa for the 'best state' was 0.83 (SE=0.05) and 0.96 (SE=0.02) for the 'worst state'.

Validity

The correlations of the PALOC-s score of the fifth observer with the WNSSP% and the DRS are presented in Table 3. On all 100 observations, the correlations with the WNSSP% varied between 0.93 and 0.91 and with the DRS the correlations varied between 0.85 and 0.86. All correlations were significant at the .01 alpha level.

Table 2. Inter-observer agreement scores (κ_w) between the six pairs of observers on the draft version of the PALOC-s

Pairs of observers	κ_w general	*SE* κ_w general	κ_w best	*SE* κ_w best	κ_w worst	*SE* κ_w worst
1 x 2	0.93	.02	0.87	03	0.90	.04
1 x 3	0.95	.01	0.89	.02	0.95	.02
1 x 4	0.90	.02	0.85	.04	0.88	.04
2 x 3	0.93	.02	0.92	.02	0.89	.04
2 x 4	0.91	.02	0.92	.03	0.92	.03
3 x 4	0.92	.03	0.89	.03	0.92	.04

PALOC-s

In three of the four subgroups of observations, the correlations with the WNSSP% scores varied between 0.89 and 0.92, while the correlations with the DRS varied between 0.75 and 0.86. All these correlations were significant at the .01 alpha level.
In the fourth subgroup of observations the correlations showed considerable variance, without attaining significance. This subgroup, however, consisted of only four (4) patients.

To control for any bias in the selection of all 100 observation tapes, an analysis was performed of the distribution of the scores on the 'general state' of the PALOC-s by the fifth observer. Table 4 shows that in the first three subgroups of independent observations, the distributions were very similar. Data from the very small fourth subgroup are not presented.

Table 3. Correlations (r_s) of the score of the fifth observer on the PALOC-s with the WNSSP% and the DRS, in all observations together, as well as in subgroups with independent observations (nR = number of ratings)

Groups	*WNSSP% x* 'general state'	*DRS x* 'general state'	*WNSSP% x* 'best state'	*DRS x* 'best state'	*WNSSP% x* 'worst state'	*DRS x* 'worst state'
All ratings (nR=100)	0.93**	0.85**	0.91**	0.86**	0.92**	0.85**
1 (nR=44)	0.91**	0.88**	0.88**	0.86**	0.92**	0.86**
2 (nR=36)	0.92**	0.80**	0.90**	0.84**	0.91**	0.81**
3 (nR=16)	0.91**	0.76**	0.90**	0.81**	0.89**	0.75**
4 (nR=4)	0.26	0.82	0.90	0.71	0.26	0.81

** $p < .01$ (2-tailed)

Table 4. Distribution of the scores of the fifth observer on the 'general state' of the PALOC-s in the first three subgroups with independent observations. In each subgroup each patient is represented only once

Groups	Lowest score	Highest score	Mean	SD
1 (nR = 44)	1	8	4.32	2.52
2 (nR = 36)	2	8	4.39	2.21
3 (nR = 16)	2	8	4.56	1.9

nR = number of ratings

To control for a possible age effect on the scores, an analysis was performed in three different age groups: 2-10 years (N=11), 11-20 years (N=22), and older than 20 years (N=11).

All correlations between the PALOC-s scores of the two observers, and between the PALOC-s scores of both observers with the WNSSP% and the DRS respectively, varied between 0.80 and 0.95. These correlations were again significant at the .01 alpha level. Therefore, no age effects on the reliability and validity scores presented in this study were found.

To further analyse the relationship between the PALOC-s and the WNSSP%, and between the PALOC-s and the DRS, a curve estimation procedure was performed. A straight line was the most appropriate fit for these relationships (Rsq = 0.89, respectively Rsq = 0.72). Higher order curves did not explain a significantly larger proportion of variance. In Figure 2, the linear regression lines show the relationships between the WNSSP% and the DRS with the scores of the fifth observer on the 'general state' of the PALOC-s.

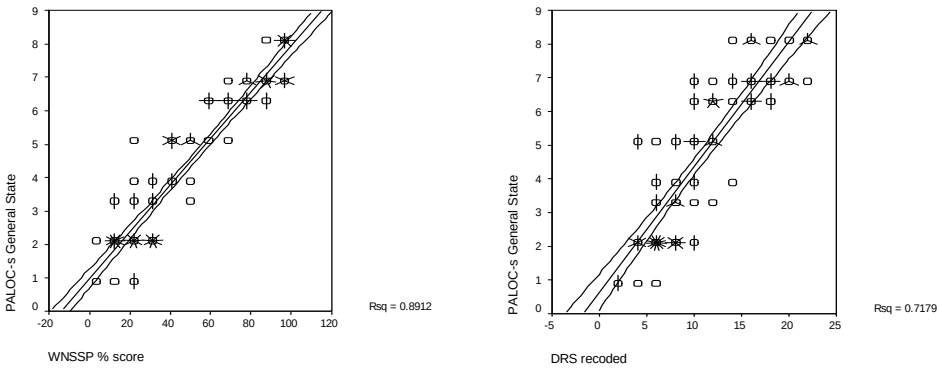

Figure 2. Individual data points and linear regression lines (including 95% CI lines) showing the relation of the WNSSP% and the DRS to the 'general state' score of the fifth observer on the PALOC-s (for comparability of the graphics the DRS-scores were recoded: a score of 1 was recoded into 29, a score of 2 into 28, etc., always summing up to 30)

Discussion

In this study, the quality of the PALOC-s was investigated in a cohort of young persons with severe brain injury. The reliability (inter-rater and test-retest reliability), the responsiveness, and the concurrent validity were all shown to be good.
As far as we know, this is the first observation scale that distinguishes among a wide range of disturbed consciousness levels, and that is based on some theoretical considerations about the concept[4,18,20,24,29,36]. Insight is increasing concerning the gradual improvement of consciousness during recovery from coma after severe brain injury[47]. A reliable and valid assessment of such a process is therefore of great importance for the clinical management of these patients[40].

Assessing levels of consciousness
The distinction between the VS and the MCS in literature is clear and increasingly undisputed[36], despite some opposing reactions[8,13,58] to one of the publications advocating this distinction[22]. One can dispute at which level the distinction has to been made between VS and MCS. The International Working Party could not reach agreement as to whether the transitional state (PALOC-s level 5) was vegetative or non-vegetative[4]. According to the criteria of Giacino et al[22], level 5 of the PALOC-s is NOT a minimally conscious level, because its description lacks any simple command following, gestural or verbal responses, intelligible verbalization or purposeful behaviour. But, as recently was stated by the Royal College of Physicians[56], the main features of PALOC-s level 5, like a smile in response to a relative, an attempt to reach out for an object (albeit in an automatic way, and not in reaction to a question) and fixating people systematically, are all incompatible with the vegetative state. Nevertheless, these behavioural features are not sufficient for classification of patients as minimally conscious. Therefore, the precise distinction between VS and MCS can still be argued. Recently, Lavrijsen identified eight patients in Dutch nursing homes without the ability to follow simple commands and who met the criteria of the 'transitional state' as described by the International Working Party[3,42]. Lavrijsen recommended classification of these patients as not being in a vegetative state and stressed the need for further research because of the medical-ethical implications. Relating the PALOC-s in different phases of recovery to long-term outcome levels, combined with modern imaging techniques, could perhaps shed more light on the question concerning which level marks the distinction between the vegetative and minimally conscious state, assuming these levels are genuine. The question whether it is possible and necessary to identify gradations within the supposed VS and the MCS, can be answered positively. At the introduction of the MCS, the Aspen Workgroup on the Vegetative and Minimally Conscious States concluded that there were no compelling arguments to divide the MCS into further gradations[20]. The results of the present study show, however, that in the MCS

there are differences in the way patients react to stimuli as given in the WNSSP protocol. The individual data points in Figure 2, showing the relation between the PALOC-s and the WNSSP, demonstrate a clear distinction between the three levels of the MCS. This is important for both clinical management and outcome research.
In the VS, the distinction between level 2 and 3 is not as clear and therefore disputable. Level 4, however, can clearly be distinguished based on the relationship with the WNSSP scores. In 1980, Plum & Posner already stated that some vegetative patients are akinetic and mute, while others may be restless, noisy and hypermobile([51] p.6). This is presumably related to parts of the brain which may have recovered either partially or fully, which can be a sign that (some) recovery is possible[43].

Location and extent of the damage, especially of diffuse axonal injury and/or of thalamic damage, may be responsible for these differences[37,52]. The less axonal damage the more recovery that may occur. Therefore, the distinction between level 3 and 4 of the PALOC-s might be crucial for prognostic reasons. Also, one can argue whether or not level 7 belongs to the MCS. As Giacino stated, the boundary between the MCS and consciousness is questionable and unclear [29]. It can be presumed that (some of the) patients at level 7 of the PALOC-s were fully conscious, but had severe cognitive and behavioural deficits. For clinical reasons, the importance of the distinction between levels 7 and 8 is the (in)ability of the patient to communicate comprehensibly[36].

Box 2.

Clinical presentation and acute management
Patient 2 is a man of 25 years of age at the time of injury. He was injured in a traffic accident, after being hit by a train. He was immediately unconscious. The initial GCS-score is unknown.
Initial CT brain scanning demonstrated a subdural haematoma in the left parietal and right frontal lobes. There were also skull fractures. Initial neurosurgical treatment consisted of the application of an intracranial pressure gauge, and a bilateral craniotomy. The haematoma was removed. In addition, an amputation of the lower limb had to be performed. Patient 2 spent 16 days in the ICU. His GCS score progressed to E2M5V1 while reacting to some stimulation.

Rehabilitation programme and progress
At admission patient 2 was in a vegetative state (PALOC-s level 3). He showed very little progress (see Figure 3). Sometimes there were responses to pain, temperature and touch. He responded by closing his eyes and making chewing movements. He often showed a distracting, gazing expression. Sometimes there was tracking of the eyes

towards objects (PALOC-s level 4). He did not show any anticipating behaviour. No progress was seen, and he was sometimes difficult to arouse.
Two months after admission to EINP he suffered a large epileptic seizure. From then on, he did not show any reaction to stimulation. He was discharged to a nursing home 111 days after admission to EINP. The PALOC-s level at discharge was 2. Patient 2 deceased 6 months later.

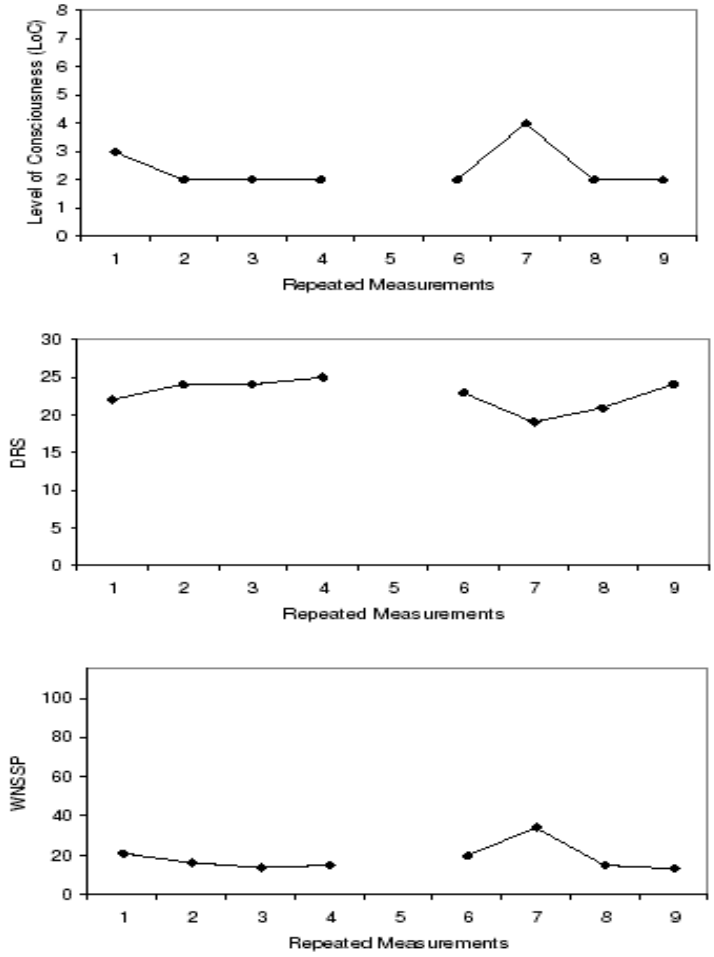

Figure 3. Graphic presentations of the PALOC-s, DRS and WNSSP-scores.

A persisting question is whether a new scale is actually necessary. An affirmative answer has been given in the recent past by the National Health and Medical Research Council of the Australian Government, stating the need for refinement of technologies to identify subclasses of unconscious patients[47]. The following scales and methods were developed to investigate patients with disturbed consciousness: the Coma / Near Coma scale (CNC) [54], the Coma Recovery Scale (CRS)[48], the Coma Recovery Scale-Revised (CRS-r)[26], the Rancho Levels of Cognitive Functioning Scale (RLCFS)[34,35], the Sensory Stimulation Assessment Measure (SSAM)[53], the Sensory Modality Assessment and Rehabilitation Technique (SMART)[30,31,64] and the Western Neuro Sensory Stimulation Profile (WNSSP)[6]. The Disorders of Consciousness Scale (DOCS) was presented recently with this same purpose[49,50]. The most important difference between the PALOC-s and the scales mentioned above, is the possibility of the usefulness of the PALOC-s in differentiating between distinct levels of consciousness from coma to full consciousness. All others scales either add up to a total score (as in the WNSSP and the CRS(-r)), or the results are partly qualitatively presented (as in the SSAM and the SMART), or the used terms and descriptions are no longer valid for the VS and the MCS (as in the CNC). A disadvantage of the SMART is that a special kit must be purchased, combined with a training program given by the developers of the SMART. The RLCFS was developed before the concepts of the vegetative or minimally conscious states were presented and results in a combination of levels of consciousness (Levels I to IV) and cognitive functioning (Levels IV to X), without a clear connection to the VS and MCS[34]. Furthermore, the RLCFS offers little sensitivity in discriminating subtle changes in the state of consciousness[7].

The second characteristic of the PALOC-s, which is not present in any of the other scales, is the possibility of scoring fluctuations of consciousness during the examination by means of the 'best score' and 'worst score'. As has been demonstrated in our data, these scores were valid and highly reliable.

In this study, the PALOC-s was scored after having administered the WNSSP first. An important question is whether the scale can be scored without a thorough examination. We did not investigate this, however we gathered the PALOC-s scores of the clinical team which were given in the same weeks as the examinations for this study were executed. All correlations between the PALOC-s scores of the clinical team and the scores of the investigator of the first ten assessments were high and significant at the 0.01 alpha level. Although the draft version of the PALOC-s was used instead of the final slightly modified version, it can be assumed that experienced clinicians are able to score the PALOC-s reliably, without first administering the WNSSP.

Limitations

The method used here to investigate the reliability of the PALOC-s, is generally applied in other studies for these kinds of scales[1,33,63]. We decided, however, to adapt the initial descriptions of some levels based on the experiences of the four observers. Subsequently, it was necessary to extend the study with two more observers to establish the reliability and validity for the definite form of the PALOC-s. Two observers are generally not sufficient in investigating the reliability of such a scale. However, the changes made to the draft version of the PALOC-s were minor, which leads us to conclude that reliability scores of the draft were indicative of the reliability of the final version. This is further demonstrated by the strong correlation between the scores of the first four observers and the scores of the fifth and sixth observers on the general state of the PALOC-s.

To investigate the validity of a new observation scale, the construct validity should be considered first [45]. One of the possibilities is to relate the observed level of consciousness to neurophysiological parameters which are supposed to reflect the level of activity of the brain. For instance, electrodermal activity (EDA) [10], evoked or event related potentials (EP) [14,32], PET-scan or functional magnetic resonance imaging (fMRI) [40] could be used. In a clinical situation with brain injured patients, however, either the technique is too difficult to execute (as is the case with fMRI) or it cannot be conducted because it requires some patient cooperation (as is the case with all techniques). For this reason we compared other observational scales which are supposed to give insight into the level of consciousness with our new scale with.

Box 3.

Clinical presentation and acute management

Patient 3 is a boy of 6 years old at the time of injury. He nearly drowned in a small lake during an outing with his family. He was pulled out of the water after at least fifteen minutes. He was immediately resuscitated by paramedics for about nine minutes. At admission to the hospital, the GCS score was E1M3Vt. He suffered hypothermia (32 degrees Celsius), and after warming up he developed a fever. Initial CT brain and MRI scanning demonstrated diffuse hypoxia and anoxia, and a diffuse white matter lesion. Patient 3 spent 8 days at the ICU. He was transferred to EINP 56 days after injury.

Rehabilitation programme and progress

Patient 3 was in a vegetative state during admission to EINP (PALOC-s level 3, see Figure 4), sometimes showing spontaneous motor activity. Initially it was unclear if there were auditory problems. He generally did not respond to auditory stimulation, although he showed some signs of recovery of consciousness. Gradually, patient 3 made

progress. His level of consciousness improved and after two months, he was able to handle some simple therapeutic exercises(PALOC-s level 6). However, his behaviour appeared to be automatically triggered. He was especially focused on people and moving objects. Sporadically he spoke a few words. He often smiled when others talked to him. He was easily distracted, and showed some functional problems.
Although his level of consciousness progressed, patient 3 showed a disturbed pattern of information processing. In addition, he suffered from dyspraxia.
He was discharged to a regular rehabilitation facility at 83 days after admission to EINP. The PALOC-s level at discharge was 6 and the DRS-score was 19. Seven months after discharge, the DRS-score was 11.

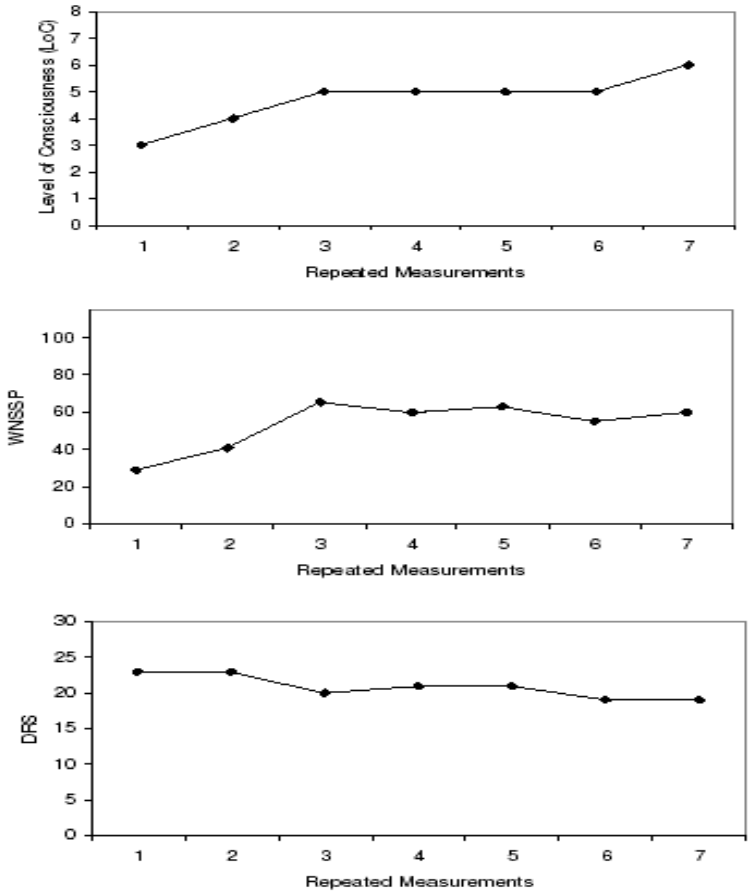

Figure 4. Graphic presentations of the PALOC-s, WNSSP and DRS scores.

Another problem in this validation study was the small number of subjects.
The only possible way to accomplish a desirable subject group larger than the available 44 patients was to include multiple observations of the same patient. This method of investigating the validity of a scale is somewhat unusual but not unique[30,44,60]. The procedure resulted, respectively, in high correlations between the PALOC-s with the WNSSP and DRS scores. The correlations in the independent subgroups of patients were high as well. This being true for all subgroups except the smallest one. After taking a closer look, the raw data showed that this was due to the scores of only one patient. Therefore, the information from this subgroup does not threaten the general conclusion being that the validity of the PALOC-s is high.
Finally, due to the nature of admission criteria to EINP, this study was executed with a cohort of patients up to 25 years of age. Although it can be assumed there will be little difference in the way unconscious adults above the age of 25 react, compared to young adults, further research is necessary to confirm this.

Future research

The relationships between the levels of the PALOC-s and neuropathological and neurophysiological variables should be investigated in future research, to obtain more clarity concerning the significance of the different levels.

In addition, it is important to investigate the predictive power of the PALOC-s, especially for the 'best' and 'worst' scores. Finally, confirmation is needed about the assumption that the PALOC-s also is reliable and valid for adult patients. It is therefore important to repeat this study with patients older than 25 years.

General Conclusion

The development of a level-of-consciousness scale for patients with a disturbed level of consciousness is a difficult task. Generally, only small numbers of patients can be included, sufficiently experienced independent observers are scarce, and a golden standard is nonexistent to compare the new data with. In this study, to our knowledge, the best possible solutions for these problems were chosen. This resulted in the presentation of a reliable and valid scale, the PALOC-s, to determine the level of consciousness in (young) patients with disturbed consciousness after severe brain injury. The PALOC-s should be scored after a structured assessment by experienced and trained staff members. Until further research can confirm or deny these findings, the PALOC-s offers the opportunity for clinical teams in hospitals and rehabilitation centres to evaluate the course of recovery for patients with a disturbed level of consciousness in the post-acute phase.

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APPENDIX

Examples of changes made in the description of sublevels 6 and 7

First version PALOC-s	Final version PALOC-s
Inconsistent reactions Occasionally obeying simple commands. Total dependency. *The patient has obvious cognitive disturbances and is unable to think comprehensively*.	**Inconsistent reactions** Occasionally obeying simple commands. Total dependency. *The patient has profound cognitive limitations; neuropsychological testing is impossible. Level of alertness fluctuates, but is generally low*.
Consistent reactions The patient obeys simple commands. Many cognitive disturbances remain. Total dependency.	**Consistent reactions** The patient obeys simple commands. *Alertness level is high and stable*. Many cognitive disturbances remain. Total dependency.

Italics indicate changed and/or added text

CHAPTER 3

Incidence of young patients in an unconscious state one month after severe traumatic brain injury: a population study

Submitted for publication
H.J. Eilander, M. Heutink, E.J. Schouten, P.L.M. de Kort, C.M. van Heugten, D.A. Bosch, A.J.H. Prevo

Abstract

An early intensive neurorehabilitation programme (EINP) for young patients in prolonged vegetative (VS) or minimally conscious state (MCS) after severe traumatic or non-traumatic brain injury was developed in the Netherlands twenty years ago. A case-control study was set up, in order to evaluate the efficacy of EINP. A retrospective survey was executed in all 24 major hospitals in the Netherlands, which admit young patients with severe brain injury. Twenty-three hospitals co-operated. In the survey patients under the age of 25 who suffered severe traumatic brain injury (TBI) in the period between December 2000 and June 2003 and were hospitalized for at least one month, were searched for.
Using the hospital registration systems, in total 206 patients could be traced. Only 42 patients appeared to be still in VS or MCS after 30 (±3) days. Therefore, the incidence of patients with TBI under the age of 25 still unconscious after one month, was 3.4 per million population (PMP) per year. This is much less than anticipated given the results of previous publications. Because 30 patients out of the group of 42 patients had been admitted to EINP, only 12 patients could participate in the control group. This number is far too small to make any reliable comparison with the EINP group; therefore the case-controlled study was discarded.

Keywords

Children
Incidence
Minimally conscious state
Traumatic brain injury
Vegetative state
Young adults

Introduction

Severe traumatic brain injury (TBI) may lead to prolonged loss of consciousness and long-term mental and physical consequences[1]. The course of recovery of consciousness is often slow, progressing through different levels of consciousness: the vegetative state (VS)[11] and the minimally conscious state (MCS)[9], both with three sublevels. When the VS or MCS lasts more than one month, chances for full recovery are very small[13,14]. Many of these surviving patients remain care-dependent for the rest of their lives[4].
The incidence and prevalence of prolonged unconsciousness after severe TBI is not well known, due to definition problems, changing medical practice over time, misdiagnosis, differences in rates of TBI between countries and the lack of adequate registration systems[2]. Jennett[11] calculated for three different countries an incidence of VS, one month after the injury, between 14 and 67 per million population (PMP), with a proportion of children between 6% and 38% (the range was partly caused by different age limits used). In the Netherlands, in a survey in all nursing homes over a period of 2.5 years, only 32 patients between 9 and 90 years were identified being in VS, 87% for more than 12 months[12].
The incidence and prevalence of patients in MCS is unknown[9].
Rehabilitation treatments for patients in VS or MCS are recognized for the last twenty years. However, until recently the effects have not been demonstrated[8]. In 1987, EINP for children and young adults (0-25 years) was developed in the Netherlands[7]. Patients were admitted to EINP between one and six months after injury, still in VS or MCS. An evaluation study showed positive long-term effects, compared to earlier outcome studies[5]. Two-thirds of all patients recovered into consciousness and most of them were able to live partially or fully independent. To create a control group of patients who were not admitted to EINP, and to get an estimation of the facilities required for future treatment, a survey was executed in all Dutch major hospitals with neurosurgery intensive care units (ICU's).

Methods

In the Netherlands the acute hospital care for young patients with severe brain injury is concentrated in 24 major hospitals. In 23 of these hospitals medical specialists were willing to co-operate in retrospective identification of all TBI patients, who remained unconscious after being hospitalized for more than one month in the period between December 2000 and June 2003. The inclusion criteria were: TBI, Glasgow Coma Scale[15] score at admission to the emergency unit ≤ 8, age < 25 years, and in VS or MCS at 30 (± 3) days after injury. All patients who fulfilled all inclusion criteria, except the last one, were identified using the hospitals' registration systems. Secondly, the medical files of all the identified patients were carefully examined to determine the level of consciousness at 30 days (± 3) after injury, using the Post-Acute Level Of Consciousness scale[6].

Results

Scanning of the registration data of the 23 hospitals resulted in 206 patients found in 19 of the hospitals. In four hospitals no patients were found. After thorough examination of the files of these 206 patients, 42 of them proved to be in VS or MCS at 30 days (±3) after injury. Therefore, these findings show that the incidence of young patients in a VS or MCS at one month after TBI is 16.8 per year. Given a total population in 2001 of 4.870.196 persons between 0-25 years[3], this results in 3.4 PMP. Of the 42 patients found, 30 had been admitted to EINP, resulting in only 12 patients who could participate in a control group. Because any reliable statistical comparison with the group treated with EINP was ruled out, the aimed control study had to be terminated.

Discussion

In this study we tried to create a case-controlled group in order to evaluate the effectiveness of EINP for young TBI patients still in VS or MCS one month after TBI. Because the incidence of TBI in the period between December 2000 en June 2003 remained far below expectation and the majority of the patients had been admitted to EINP, it was impossible to create such a case-controlled group. Therefore, the effectiveness of EINP can only be examined by comparing the outcome results with previous data, for instance as published by the Multi-Society Task Force on Persistent Vegetative State[13,14].

The small number of young patients in a prolonged vegetative or minimal conscious state after severe brain injury found in this study, is in concordance with the total number of patients in VS in Dutch nursing homes[12]. However it is much smaller than expected based on the calculations of Ashwal[1].These calculations resulted in an estimated average of 151 VS patients less than 15 years of age (range 18-246) in the Netherlands. Worldwide, according to the calculations, the average prevalence of children in VS was calculated as 49 PMP (6-80). In our study, the numbers included not only patients in VS, but also patients in MCS. These findings indicate that the incidence of VS is even less than 3.4 PMP. Due to legal-ethical restrictions caused by the obliged termination of the control study, it was not permitted to use the collected data. Therefore, it was not possible to make a distinction between the numbers of patients in VS and those in MCS.

As far as we know, this was the first study ever conducted in which, during a given time period, the total number of young patients in a prolonged vegetative or minimal conscious state in one country was identified. The results show that calculations based on statistical formulas are generally imprecise and tend to overestimate. It can be assumed that not all necessary features are incorporated in these formulas. It can also be assumed that the definition of the vegetative state has changed dramatically over the last decade after the introduction of the concept of the minimally conscious state[10], resulting in a considerable drop in the numbers of patients in vegetative state.

Incidence

Although incidence and prevalence rates seem to differ between different European countries, it can be assumed that the data found in this study are also applicable to other western countries. By using the ratio between the countries in the data presented by Ashwal in 2005, calculations can be made for all the countries that were included in that study[1]. It is strongly recommended to execute new incidence and prevalence studies in different countries, in standardized age groups and using a uniform set of instruments to determine the different causes, the injury severity, and the levels of consciousness.

The results of this study make it possible to calculate the number of beds needed to provide EINP to all possible patients in the Netherlands. These calculations are important for the planning of health care facilities. The mean admission period to EINP in the past years was 3.6 months. Therefore, it is estimated that it is necessary to create facilities for 5 patients (16.8 / 12 / 3.6 = 5.04) to provide EINP for all young TBI patients less than 25 years of age. Knowing the ratio between TBI and non-TBI patients (about 2:1 for all age groups under 50), as well as knowing the population ratio's[3], the total number of beds in the Netherlands required for patients who meet the admission criteria for EINP can be calculated as 8-10 for patients under 25 years and as 12-15 for patients between 25 and 50 years of age.

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CHAPTER 4

Children and young adults in a prolonged unconscious state due to severe brain injury: Outcome after an early intensive neurorehabilitation programme

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Abstract

Primary objective
The rehabilitation centre Leijpark (RCL) in the Netherlands provides an Early Intensive Neurorehabilitation Programme (EINP) to children and young adults in a prolonged unconscious state after severe brain injury. In an extensive research project the effects of EINP were studied. This part of the project focused on the outcome in terms of level of consciousness (LOC) in relation to the specific characteristics of a retrospectively studied cohort.

Research design
This study was executed according to a one-group archived pretest-posttest design.

Subjects
Subjects were all consecutively admitted patients (n = 145, 72% male) between December 1987 and January 2001. Inclusion criteria were: age 0-25 years, within 6 months after injury, LOC at admission vegetative state (VS) or minimally conscious state (MCS). 104 patients (72%) suffered a traumatic injury and 41 patients (28%) a non-traumatic injury.

Methods and procedures
All patients had received EINP until they reached consciousness, or until it was concluded that no progress was achieved during three months after the start of EINP. Medical files were investigated to collect the patients' characteristics and injury data, to determine the LOC at admission and at discharge, and to determine the discharge destination.
Results
Almost two-thirds of the patients reached full consciousness. LOC at admission, aetiology, and interval since injury were found to be significant prognostic factors. Traumatic patients had a much better outcome than non-traumatic patients. A comparison with earlier outcome studies showed a more favourable outcome than expected. It is argued that a multicentre study is needed to confirm possible effects of EINP.

Introduction

Brain injury in children and young adults is frequently encountered in clinical practice. Such injuries can have a huge lifelong impact on the patients[34] and their relatives[29]. In the Netherlands, each year around 200-250 children and approximately twice as many young adults suffer from a severe brain injury. The mortality rate of these patients within the first year is high and most survivors suffer from serious physical, cognitive, and behavioural consequences. Some patients do not regain full consciousness within the first weeks or months after the injury and remain in a vegetative state (VS) or in a minimally conscious or low awareness state (MCS)[2,21,23] for months or even years. Research on outcome after severe brain injury shows that the chance of recovering full consciousness and regaining independent functioning is low. In 1994, the Multi-Society Task Force on Persistent Vegetative State (MSTF) used all published reliable outcome studies (all in the United States) of children who were in a vegetative state after traumatic brain injury (TBI) for at least 3 months to compute outcome chances. The results indicate that at 12 months, the chance is 14% of the patients being deceased, 30% to be still in a vegetative state; 24% of having regained consciousness but with severe disabilities; and 32% of show moderate disabilities or a good recovery[40,41]. Of the children who suffered a non-traumatic brain injury (NTBI), the chance of recovering to a conscious state (albeit minimal) is 3%, and the chance of ever being able to function at an independent level is zero.
In the last decade, evidence for human neuroplasticity has been accumulating, including evidence for the development of new neurones from stem cells[5,7,25,53,54]. Furthermore it is acknowledged that environmental input and exercise can influence the anatomy and physiology of the (human) brain, even when it is injured[4,19,42,46,54].
Ever since the early 1960s, treatment programmes have been developed aimed at restoring consciousness[16,17,23,44,47,51,58-60]. Most of the programmes are based on principles of recovery of brain function by regulated stimulation of the senses. The effectiveness of these programmes has never been demonstrated[8,14,20,35]. A major problem in evaluating comprehensive clinical treatment programmes is the control group dilemma[49]. Legal and ethical considerations, and practical problems make it difficult to use a randomised control group design. Especially family members can be expected to oppose a random attribution of the patients over the experimental and the control group. Also the complicated character of the treatment programmes makes it difficult to control for all variables. Only a long-lasting nation-wide multicentre study, in which a sufficient amount of patients can be included and in which it is possible to control for all important treatment variables, may make a control group design feasible.

In 1987, a comprehensive early intensive neurorehabilitation programme (EINP) for children in a VS or an MCS was developed at the Rehabilitation Centre Leijpark (RCL) in the Netherlands. It was based on a wide set of principles: the principle of effects of sensory deprivation opposite to stimulation[3,48], the principle of developmental resemblance of recovery

processes of all vegetative, sensory, motor, and psychological functions[56], the principle of involving families in the treatment process[6], and the principle of centrally steered transdisciplinary treatment[9,37].
In 1994, following the recommendations of Ylvisaker[61], a specialised team was created and EINP was formalised by a written protocol.
The retrospective outcome study described here is part of a larger research programme that has been developed in order to evaluate the effects of EINP. Although this study lacks a control group, the data are of interest, giving insight in the characteristics of a large cohort of consecutively admitted patients, and offering the opportunity to compare the outcome data with some earlier outcome studies. This is the first study of this size ever done in Europe.

In the present report first the results of a cohort of 145 patients will be presented in terms of level of consciousness (LOC) at admission and at discharge, and their discharge destination. Secondly, we will identify subgroups (e.g., traumatic or non-traumatic, age) and variables (e.g., LOC at admission, time interval between injury and admission) to determine whether any prognostic variables to the LOC at discharge can be identified. Finally we will compare the outcome data with some existing data from the literature.

Method

Treatment Programme
The Early Intensive Neurorehabilitation Programme (EINP) was applied to children and young adults up to 25 years of age, in a vegetative or minimally conscious state, starting as soon as possible after leaving the intensive care unit, but in any case within six months after the injury (since September 1995 within three months in case of a non-traumatic cause). The programme was carried out for three months, or for a shorter time when recovery of consciousness has occurred. In case of signs of recovery of consciousness, the total programme gradually changed into a cognitive learning programme, taking into account the individual needs and possibilities of the patient. The basic philosophy of the programme was, that an active approach may induce recovery of brain functions in many severe injured patients, but only when all important health threats are identified and treated[63], and when known principles of development and growth of brain tissue are taken into account[27].
The treatment programme focused on several domains:

- Improving the metabolic state, the state of nourishment, respiration, and skin condition, as well as diminishing the risk of infections[43]. The actual treatment activities depended on the individual situation of each patient. Special attention was given to removing invasive devices, like a tracheostomy tube or a bladder catheter.
- Recovery of the normal circadian cycles by offering a homelike environment, that was structured and filled with daily activities[48].
- Improving arousal and awareness by structured stimulation of all sensory modalities (vision, hearing, smell, taste, touch, posture and motion, pain, and temperature) in such a way that maximal arousal was generated[3]. As soon as the

patient showed any voluntary reactions, reflecting a change from VS into MCS, the programme focused on stimulation and training of cognitive functions, the contents depending on age and cognitive status[51].
- Improvement of normal posture and motor activities by intensive physiotherapy, occupational therapy, and oro-facial therapy, using sitting aids, a variety of splints, and other appliances[26].
- Improvement of the capabilities of the family to cope the situation and their own feelings, by giving support, (psycho)education, training in handling the patient, and when needed, treatment[11].

Each day, five treatment activities (sensory stimulation, physiotherapy, occupational therapy, oral therapy, or activity therapy) were planned in such a way that these activities were alternated with rest, with moments of personal care, and with family visits.
Since September 1994 the programme had been executed by a specialised team, consisting of a rehabilitation physician, a neuropsychologist, a stimulation therapist, physiotherapists, occupational therapists, speech therapists, nursing staff, a social worker and activity therapists. The team worked according to a written protocol, describing all the steps in the programme from admission to discharge, and describing the outline of the content of the programme at the different stages of recovery.
Patients' condition and progress were evaluated in a weekly schedule, together with the whole team, resulting in changes in the kind and intensity of parts of the programme. When needed, changes were made on a daily basis.

Procedures and measures
This study was executed according to a one-group archived pretest-posttest design. The first author investigated the patients' medical files to collect the patients' characteristics and injury data, to determine the LOC at admission and at discharge in the rehabilitation centre, and to determine the discharge destination.
The following patient and injury data were collected:
- Gender and birth date
- Date of injury
- Aetiology
- Admission date to EINP
- Discharge date of EINP
- Discharge destination.

The aetiology was determined on the basis of the medical note and was classified into two main categories: traumatic and non-traumatic, and further subdivided into: 'traffic' or 'other' in the traumatic patients, and in: 'hypoxia', 'near-drowning', 'encephalitis', or 'other' in non-traumatic patients. It was not always clear what really caused the loss of consciousness, e.g. in case of epileptic seizures.
The LOC of the patients was based on notes and descriptions in the patients' files. First the admission and discharge reports were analysed. If reports were missing, or there was some doubt, all medical, therapists, and nursing notes were scanned and analysed.
The LOC was classified into one of the following categories: 1=conscious (only at discharge), 2=minimally conscious state (MCS), 3=vegetative state (VS).
The definitions of MCS and VS were based on the descriptions of the International

Retrospective outcome

Working Party on the Management of the VS[2] and of the Aspen Neurobehavioral Conference[23].

- Characterisation of the VS: patients have a sleep-awake pattern and the vegetative functions are generally recovered. Patients can show delayed reflex activity or generally massive extensor or startle responses. This may progress into flexor withdrawal. Patients can also show single limb responses to stimulation and sometimes withdrawal or intermittent localisation. Eventually, roving eye movements or even tracking eye movements may be seen without focussing on people or objects.
- Characterisation of the MCS: patients are awake for most of the day. At least they show more definite localisation with tracking eye movements following objects or people, and they react with emotional responses to the presence of family. Eventually, patients may respond to simple commands, but all have profound cognitive deficits. MCS patients are totally dependent on others.
- Consciousness is characterised by continuous alertness with mutual communication in a consistent manner on complex matters (regarding age), albeit with all kinds of possible cognitive disturbances.

Although no studies are known about the reliability and validity of this classification, similar procedures have been described and used in other outcome studies[21,22]. Scoring in one of the categories was only done when the described key characteristics were reported consistently. In case of doubt, the lowest category was scored. The outcome category 'deceased' was added to classify patients who died during admittance to EINP.

The discharge destination was determined from the discharge report, or in case of absence of this report, from notes, and was classified in two main categories: 'regular rehabilitation' indicating further recovery possibilities or 'no rehabilitation', indicating a halt to further recovery. The last category was subdivided into: 'long-stay home with special services for brain-injured young persons', 'nursing home', or 'back home without treatment'.

Patients

The subjects were all patients (n = 145) who were admitted to the EINP between December 1987 and January 2001. Inclusion criteria were: age 0-25 years, within 6 months after injury, LOC at admission VS or MCS. So by definition, none of the patients was able to communicate at admission. One patient was admitted at 7.57 months after injury because of a long waiting list procedure. Patients were admitted from all over the country, which is rather unusual in the Netherlands, where health care is regionally organised. Patients who were dependent on artificial respiration, on oxygen, or on intravenously administered medication were excluded. The EINP was terminated when patients regained consciousness and were admitted to a regular rehabilitation programme, or when they were still in VS or MCS three months after admission without showing any recovery. When patients showed progress in the recovery of the level of consciousness, but were unable to receive a regular rehabilitation programme, the EINP was prolonged as long as substantial progress was shown.

Retrospective outcome

Seven patients (5%) died before reaching one of the terminating criteria of the EINP. The initial Glasgow Coma Scale (GCS)[57] score was known for 108 of the patients. One had a score of 9; all the others had a score less than or equal to eight (mean = 4.59; median = 4.00; SD 1.45), so almost all patients suffered a severe brain injury. Of all the patients 72% (n=104) were males. Most of the patients (104 patients; 72%) had suffered a traumatic injury (traffic accident: 63%) , and 41 patients (28%) a non-traumatic injury (see table 1).

Table 1. Cause of injury

	Cause	N	%
Traumatic	Traffic	91	62.8
	Other	13	9
Non-traumatic	Hypoxia	15	10.3
	Near drowning	12	8.3
	Encephalitis	8	5.5
	Other	6	4.1
	Total	***145***	***100***

All but one patient were admitted within 6 months after the injury (median = 2.1 months; range = 0.70-7.57. See figure 1).

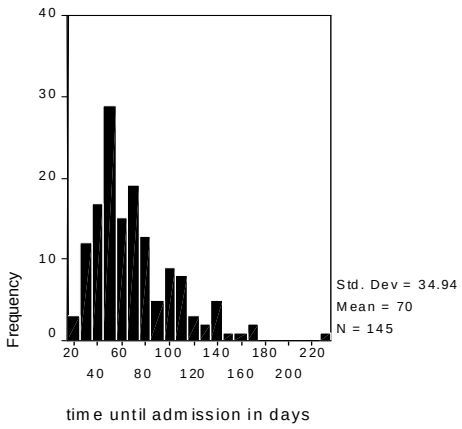

Figure 1. Time interval between injury and admission to EINP

The mean age of the patients was 12.4 years (0-25). The age distribution between the TBI and the NTBI patients was different (see figure 2).

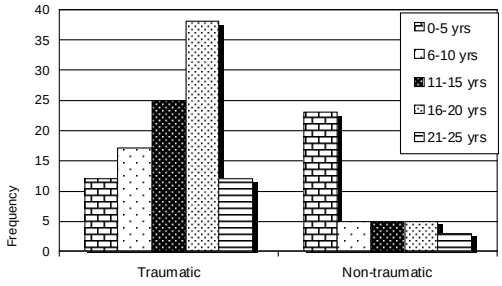

Figure 2. Age distribution of traumatic and non-traumatic patients

The mean age of the TBI patients was 14.2 years (median = 15.0 years, range 0-25 years), and the mean age of the NTBI patients was 7.5 years (median = 4.0 years, range 0-24 years).

Analyses
Data were analysed with the Statistical Package for the Social Sciences (SPSS 11.0.1, © SPSS Inc.). Descriptive statistics such as frequency tabulations were used to describe the population and the outcome figures. Association between categorical variables was tested by chi-square tests, and group differences were tested by analysis of variance.
A logistic regression analysis was performed to see whether the level of functioning at discharge could successfully be predicted by the variables 'Level of consciousness at admission', 'Type of trauma', 'Time between injury and admission', 'Age at injury', 'Gender', and 'Admission before or after start of team treatment'. For statistical reasons LOC at discharge had to be reduced to two categories: conscious or otherwise (MCS, VS or deceased). All variables were first transformed into z-scores.

Results

Admission
There was no relation between aetiology and age on one hand, and the time interval until admission, on the other hand. The interval between injury and admission was significantly longer for patients admitted before the introduction of the EINP protocol (n = 49; mean = 81.63 days; SD 38.40) compared to the patients admitted after the introduction (n = 96; mean = 64.13 days; SD 31.64). An analysis of variance revealed a significant interaction effect ($F(1,143) = 8.57$; $p<0.01$).
Discharge
The mean interval between injury and discharge was 6.60 months (SD 3.50) in the TBI group, and 6.95 months (SD 3.10) in the NTBI group.
The mean interval between admission and discharge was 4.29 months (SD 3.00) in the TBI group, and 4.66 months (SD 2.62) in the NTBI group. When LOC at admission is included in the differentiation, the following cross-table displays the mean treatment duration for each group (table 2).

Table 2. Mean duration of treatment in months, related to aetiology and LOC at admission

	MCS at admission	VS at admission	***All patients***
Traumatic	3.37	5.44	***4.29***
Non-traumatic	5.12	4.06	***4.66***
All patients	***3.86***	***5.08***	***4.39***

An analysis of variance revealed a significant interaction effect ($F_{(1,141)}=9.55$; $p<0.01$), indicating that in the TBI group the treatment duration was longer for the VS patients than for the MCS patients. In the NTBI group this was reversed: the treatment duration was longer for the MCS patients than for the VS patients.
There were no significant main effects in this analysis, so neither the LOC nor the aetiology alone contributed to the differences in duration of treatment.

Retrospective outcome

Table 3. Outcome (including deceased) related to aetiology and LOC at admission

		LOC at admission				
		Traumatic MCS	Traumatic VS	Non-traumatic MCS	Non-traumatic VS	***Total***
LOC at discharge	Conscious	51 (86%)	22 (49%)	15 (65%)	2 (11%)	***90 (62%)***
	Minimally Conscious	7 (12%)	17 (38%)	6 (26%)	9 (50%)	***39 (27%)***
	Vegetative	0	4 (9%)	0	5 (28%)	***9 (6%)***
	Deceased	1 (2%)	2 (4%)	2 (9%)	2 (11%)	***7 (5%)***
	Total	***59 (100%)***	***45 (100%)***	***23 (100%)***	***18 (100%)***	***145***

Level of consciousness
At admission, 82 patients (57%) were in an MCS and 63 (43%) were in VS.
At discharge, 90 patients (62%) were conscious, 39 (27%) were in MCS, and 9 (6%) were in VS. Seven patients (5%) died before one of the terminating criteria of EINP was reached (see table 3).
We performed two Chi-square tests for association, firstly on a 4-by-2 table, obtained by combining the MCS-scores and the VS-scores, and secondly on a 4-by-2 table, obtained by combining the traumatic scores and the non-traumatic scores. The tests revealed that patients in MCS at admission had a better chance for recovery than patients in VS at admission ($\chi^2_{(3)}=31.121$, $p<0.01$), and traumatic patients had a better chance for recovery than non-traumatic patients ($\chi^2_{(3)}=12.084$; $p<0.01$. See also figure 3).

Discharge destination
Of the 101 surviving traumatic patients, 69 (68%) were referred to a regular rehabilitation facility. Four of them were still in MCS, one infant of 2 years and three young adults who were discharged to a psychiatric rehabilitation centre.
Eleven (4 of them conscious) were discharged to a long-stay home with special services for brain-injured young persons, 12 (all in VS or MCS) were discharged to a nursing home or hospital, and 9 (3 of them conscious) went back home without further treatment. Of the 37 surviving non-traumatic patients, 13 (35%) were discharged to a rehabilitation setting (1 in MCS: a child of 5 years). Five (14%) patients were discharged to a long-stay home with special services for brain-injured young persons (1 conscious). Six (16%) patients were discharged to a nursing home or hospital (1 conscious: a young woman who was discharged to a hospital because of complications), and 12 (35%) went back home without further treatment (3 of them were conscious). Of the 22 patients who went home, 20 (91%) were under 16 years of age. Of the 44 patients who went to a nursing or long-stay home, 29 (67%) were 16 years or older.
The association between the LOC at discharge (values: 1=conscious, 2= MCS, 3=VS) and the indication for further treatment (values: 1=rehabilitation, 2=no rehabilitation) was calculated.

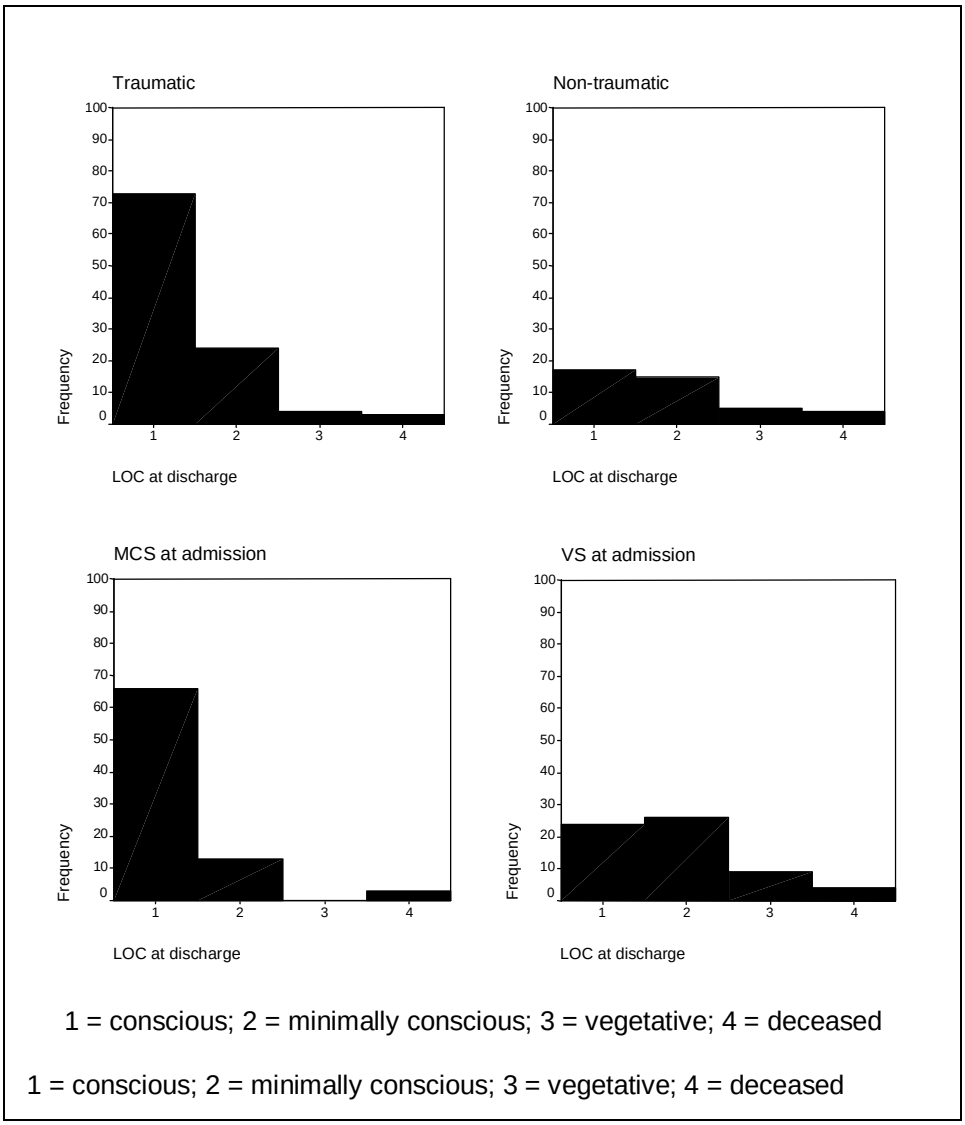

Figure 3. Level of outcome in different groups of patients

The Spearman rho equalled 0.73 ($p<0.01$), which means there was a strong association between the discharge destination in terms of treatment possibilities, and the LOC at discharge.

Prediction of level of functioning at discharge

Based on six predictors (LOC at admission, time between injury and admission, type of trauma, age at injury, team treatment,

and gender), a logistic regression analysis was performed to predict the LOC at discharge in terms of 'conscious' or 'not conscious'. A test of the regression model containing all six variables against a model containing the constant only revealed a highly significant result: $\chi^2_{(6)} = 56.25$ ($p<0.001$). Thus the predictors as a set distinguish successfully between the patients who regained consciousness and those who did not. The proportion of variance explained by the model (Nagelkerke's R^2) was equal to 0.44, while 62% of the cases could be classified correctly for the non-conscious outcome category, and 88% for the conscious outcome category. Comparison of this classification with the chance classification of success of 50% was again highly significant ($z=6.72$; $p<0.001$). Further analysis revealed that, of the six predictors, three contributed significantly to the prediction of the LOC at discharge. The level of consciousness at admission to the rehabilitation centre clearly was the most important one: the odds of being conscious at discharge were more than nine times higher for those being in MCS at admission as compared to those being in VS ($\chi^2_{(1)}=29.14$; $p<0.01$; odds-ratio = 9.54; CI_{95}= 3.85 - 23.64). The next important variable was 'Type of trauma'. Traumatic patients had a six times better perspective than non-traumatic patients ($\chi^2_{(1)}=11.77$; $p<0.01$; odds-ratio = 6.04; CI_{95}= 2.06 -17.73). 'Time between injury and admission' was the least important predictor. A one-unit increase in time until admission (in terms of z-scores) was associated with a likelihood of becoming conscious that was about half as high ($\chi^2_{(1)}=13.02$; $p<0.01$; odds-ratio = 0.43; CI_{95}= 0.26 - 0.71). So when time until admission increased, the chances of regaining consciousness decreased significantly. The variables 'age at injury', 'team treatment', and 'gender' separately did not contribute to the LOC at discharge.

Discussion

The aims of the present study were twofold. Firstly, we were interested in the characteristics of the cohort and in the outcome figures in terms of LOC and discharge destination. Secondly, we tried to identify variables that could predict the recovery possibilities.

The distribution between TBI and NTBI, and the distribution between male and female in our cohort, reflect what is generally found in epidemiological studies[18,52]. It also is of no surprise that in the youngest children, non-traumatic injuries are the majority, nor that the adolescents showed a peak of traffic accidents[28]. We can therefore conclude that the studied cohort is a representative sample of young persons with a severe brain injury.

The cohort can be considered as having severe brain injury, as shown by the known GCS-scores. Although the GCS-score was unknown of 37 patients, it appeared that the percentage of VS patients at admission in this group was higher than in the group with a known GCS-score (51% compared to 41%), indicating an even more severe level of brain injury. In severe brain-injured patients, the outcome is expected to be

poor, related to recovery of consciousness[45], as well as to recovery of function[38]. Nevertheless, the outcome figures show that a majority of the patients underwent a substantial recovery, although some patients did not show any recovery at all.

To compare this study with earlier outcome studies, we found one outcome study of Boyer and Edwards, describing a similar treatment programme for children and adolescents with TBI[9]. Of the 83 patients in that study who were still in VS after 3 months, 43 % were in VS at one year. In our study, only 5.4% were in VS at discharge at a mean of 8.66 months (median = 7.85; SD 3.59). Ten years ago, the Multi-Society Task Force (MSTF)[41] computed the outcome chances for different categories of patients who were still in a VS at 3 months after injury, based on all available outcome studies. In our study, 39 TBI patients and 21 NTBI patients were still in a vegetative state three months after injury. According to the MSTF, TBI patients have a 14% chance (CI_{99} = 1 - 27) of dying, and a 30% chance (CI_{99} = 13 - 47) of staying in VS. In our study, none of these patients died, and 5% (CI_{99} = 0 - 14) remained in VS. The NTBI patients' chance of dying, as calculated by the MSTF, is 3% (CI_{99} = 0 - 11), and the chance of remaining in VS is 97% (CI_{99} = 89 - 100). In our study 10% (CI_{99} = 0 - 26) died and 19% (CI_{99} = 0 - 41) remained in VS. As can be seen, the outcome percentages between the MSTF calculations and our results differ significantly in two categories; in one category there is a small overlap in the 99% confidence intervals. Only the percentage of NTBI patients that died corresponds fully with the computed chances. So, the patients in our study generally had a more favourable outcome than predicted by the MSTF. In a series of studies, Kriel et al. described the outcome of a total of 188 children and adolescents with severe brain injury, traumatic and non-traumatic, who had been admitted to an in-patient brain injury rehabilitation service at a regional specialty hospital for children[30,31,33]. Sixty (65% TBI) were in VS at least three months after injury. Six months after injury, 67% of them were still in VS, and only 17% were fully conscious (could communicate). At 12 months after injury, 45% were in VS, and 23% were fully conscious. In our study, 42 (64.3% TBI) children and adolescents were still in VS after three months. The mean discharge from EINP in this group is at 8,14 months (median = 7.53; SD 3.80) after injury. At discharge, 19% had died or were still in VS, and 45% were fully conscious. In some older studies, outcome percentages of children (in TBI) who remained in a VS vary between 11% and 35% [10,55]. In one study on NTBI patients, 80% remained in a VS[24]. So, compared to earlier studies and to the computed outcome chances by the MSTF, in our study the outcome seemed to be more favourable. This counts for TBI patients as well as for NTBI patients. We could not find any study with outcome results of comparable patients that surpass our study. We do not know what caused the more favourable outcome in our study. A possible explanation is the use of the EINP, which has been developed to improve and accelerate recovery possibilities. However,

it should be taken into account that the differences in outcome between our study and the other reported studies can be the result of unknown differences in extent of injury, secondary damage, differences in (initial) medical care, and finally chance. Our findings are remarkably similar to those reported by Giacino and Kalmar[22], who studied a group of 104 adults with equal proportions of TBI and NTBI patients in a VS or an MCS. These patients were also admitted to a rehabilitation-based coma intervention programme. Although the authors did not describe the programme, we assume a lot of similarity between both programmes In the Giacino and Kalmar study, the outcome was measured by scoring the Disability Rating Scale (DRS) on admission and at 1, 3, 6, and 12 months after injury. At 6 months (comparable to the mean discharge time in our study which is 6.59 months after injury; median = 5.90; range 1.61-17.84 months), the mean DRS-category scores in the different patient groups are comparable to the LOC scores in our study. The similarities between both studies confirm the conclusion of Giacino and Kalmar that their findings are of clinical importance. "*Prognostic specificity, the importance of accurate differential diagnosis, and the end-of-life decision making*", are all enhanced by the similarity of the results. Especially the fact that in children and young adults the same trends are visible as in an adult group, is of importance.

The comparison our study with other outcome studies on children and adolescents, and with the outcome study by Giacino and Kalmar concerning adults, leads to the conclusion that there may exist an indication of a beneficial effect of rehabilitation programmes. Nevertheless this has to be proven definitively in a future study following a control-group design. We agree with Giacino and Kalmar's conclusion that the only way to execute such a study is "to initiate multicentre collaborative studies capable of enrolling high numbers of patients" (pp.48)[22].

As could be expected, we found a strong association between the discharge destination in terms of treatment possibilities and the LOC at discharge. Nevertheless, we were surprised to see that some patients in an MCS were discharged to a rehabilitation facility, whereas some conscious patients were not. A further analysis revealed that this discrepancy between LOC and discharge destination is present especially in the younger children. Sometimes children who were determined conscious went home, combined with some day care facility. On the other hand, some infants did get the benefit of the doubt and were referred to a special rehabilitation facility for infants. Perhaps regional differences in the facilities played a role.

Most of the youngest patients who did not receive further rehabilitation went home, whereas the oldest patients generally went to a long-stay facility. These findings are comparable to the findings of Boyer and Edwards[9], who concluded that the combination of older parents and heavier patients makes home care more difficult. Referral patterns seem to have changed over the years. Before the start of the formal procedures the majority of patients

(67%) stemmed from the immediate vicinity of the hospital whereas in later years the rehabilitation centre was more known all over the Netherlands. So then, the majority of the patients (66%) stemmed from other parts of the country, sometimes preventing patients from going home in the weekend. This could have an effect on MCS patients, most of whom are more comfortable when they are able to stay at home in weekends.
The interval between injury and admission was not related to aetiology or age. Comparison of the patients who were still in VS at admission to the patients who were already in MCS, revealed that the mean interval was slightly shorter in the latter group (66 days to 76 days). It is possible that a longer interval was caused by medical complications, but generally referral to EINP and waiting time were obviously influenced by other more coincidental factors. Introduction of the formalised protocol of EINP, combined with public announcement, reduced the interval substantially. The familiarity with EINP of hospital specialists, the Dutch family organisation, and other key figures was probably the most important factor. One can conclude from the mean treatment interval of 4 months that the EINP generally is a relatively short-term therapy, unlike some other recovery stimulation programmes[15,16].
It was unexpected to see that non-traumatic patients who were in a VS at admission had a shorter period of EINP-treatment compared to non-traumatic patients who were in an MCS at admission, whereas the figures for traumatic patients show the opposite pattern. As far as we know we are the first to reveal this pattern. The underlying mechanism might partly be explained by the far higher chance that vegetative TBI patients have to become low aware and eventually conscious, compared to NTBI patients. When vegetative patients showed any recovery of the LOC the treatment was continued until full consciousness was reached, thus explaining the long total treatment duration time for this group. It might also be explained by the fact that the non-traumatic MCS patients have fewer possibilities to recover well, because extensive diffuse brain injuries result in a slow recovery pattern[50]. In such cases, the treatment often is continued for a longer period, trying to make use of all recovery possibilities the patient may have, until a certain plateau is reached.
The data analysis revealed that LOC at admission is the most important predictive factor to the LOC at discharge. This is not surprising, assuming that some recovery already had begun in these patients. Furthermore, the results showed that traumatic patients who were already in MCS at admission had an almost 90% chance to recover consciousness, especially when admitted as quickly as possible. As the MSTF calculations have already shown, TBI patients have a much higher chance to recover to a good outcome level than NTBI patients[41]. Underlying pathology is thought to be the main cause: in the case of non-traumatic injuries, the diffuse damage affects all parts of the brain, whereas in traumatic injury, large parts of the brain are undamaged and can become functional again. Especially when the subcortical white

matter or the major relay nuclei of the thalamus are profoundly damaged, recovery seems impossible[1]. This is probably the case more often in NTBI patients than in TBI patients.
Because almost all of these patients needed further intensive rehabilitation to return to some participation in society, early admittance to a rehabilitation centre is important[9,61]. As we have shown, the shorter the interval between injury and admission, the greater the chances of recovery. Furthermore, the sooner rehabilitation is started, the fewer patients are at risk to develop unwanted behaviours caused by recovery-induced agitation[13] and the better the different treatment goals can be co-ordinated[62].
However, one may wonder about the experienced quality of life of the patients who recover to consciousness but fail to regain full independence. Earlier studies have demonstrated that patients generally have poor quality of life[12], with indications that early treatment with a formalised programme like the EINP can positively contribute to the level of discharge destination[36] and so to the quality of life. When patients are able to live in a (semi-)independent facility, they generally experience better quality of life compared to patients who are fully dependent and live in a facility like a nursing home.
The logistic regression analysis did not show any effect of the team treatment with formal procedures on the outcome, although in earlier publications the importance of a formalised programme was emphasised [9] Apart from the possibility that this absence of an effect is real, a possible explanation is that the informal procedures and the co-ordination before the formation of the team of specialists were already executed in the same way as after formalisation of the procedures. Another possibility is that the patient groups before and after the start of the team programme were not comparable. For instance, no match could be made on medical complications during admission to the hospital because of missing data in the patients' files. It is therefore possible that the two groups differed in recovery possibilities because of underlying physical problems.
Finally, we did not find an effect of age on the LOC at discharge. This seems contrary to some general ideas of better recovery chances for the very youngest children. However, as has been reported, young children with severe brain injury probably have worse chances for good recovery[32,39]. In both studies, long-term functional outcome measures have been used, while in our study we only described the LOC at discharge. Consequently it still is possible that, in further recovery and development, the youngest children in our cohort appear to have fewer possibilities, because of structural damage to brain regions important for learning.

Methodological considerations
The reliability of the procedure of retrospectively determining the LOC at admission and at discharge based on patients' files can be questioned. Information in the files was often incomplete. Not all the signs and symptoms important for the determination of the LOC were always reported.

Determining LOC thus might have been subject to interpretation errors. In addition, the author who determined the LOC at admission and at discharge was, in most cases, one of the main therapists of the patients and for long periods, the team co-ordinator. Consequently, there is a chance of biased judgement. Nevertheless, some of the recorded information is objective, i.e., the discharge destination. This feature correlated highly with the determined LOC at discharge, indicating a rather reliable judgement of the LOC.
Another issue that has to be taken into consideration is whether the categories used (VS, MCS, and consciousness) are well described and clearly distinguishable. In recent history, it has been proven to be very difficult to come to an agreement on the description of terms and levels of (un)consciousness and on recovery patterns when a group of specialists is asked to do so[2,23]. As far as is known now, no reliability study has been done on this classification of levels of consciousness. Further research on the use of this classification as a clinical scale is needed. Nevertheless, most of the time, therapists do not differ substantially when asked to evaluate patients' LOC in terms of the classification. So, the classification used at this moment is the next-best solution to describe levels of consciousness.
Conclusion and recommendations
In this study, the level of consciousness of severe brain injured patients after receiving an early intensive neurorehabilitation programme exceeded the expectations based on earlier outcome studies. So, despite the methodological shortcomings of this study, there are indications that the described early intensive neurorehabilitation programme contributed to the ultimate level of consciousness of some children and young adults in an unconscious state due to severe brain injury.
Patients who are admitted to a rehabilitation programme within the first two months after the injury, who are already in a minimally conscious state, or who suffered a traumatic injury have the best chance to make a substantial recovery, even to full independence. Non-traumatic patients still in VS after at least two months have little chance to recover to full consciousness.
Further studies are needed to be able to draw firmer conclusions. There is also a need for further research on the reliability of the classification of levels of consciousness used, on the long-term outcome levels, and on the perceived quality of life. However, most needed, whenever ethically and technically possible, is a controlled group study to compare treatment programmes for patients in VS or MCS, like the EINP, to non-treatment or a standard treatment.

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CHAPTER 5

Course of recovery and prediction of outcome in young patients in a prolonged vegetative or minimally conscious state after severe brain injury

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H.J. Eilander, V.J.M. Wijnen, C.M. van Heugten, M.A. Croon, P.L.M. de Kort, D.A. Bosch, A.J.H. Prevo

Abstract

Objective
Investigation of the course of recovery to consciousness after severe brain injury and a prolonged period of unconsciousness in children and young adults who received a specialized rehabilitation treatment (EINP).

Methods
A cohort of forty-four patients were examined every two weeks, from registration to EINP until discharge. The level of consciousness (LoC) and the level of disability (LoD) were determined. Subsequently, the long-term LoD was obtained between 2.0 and 4.4 years after discharge from EINP for all TBI patients (N=32).

Results
Three recovery patterns could be identified: remaining in VS, slow recovery to consciousness, and fast recovery to consciousness.
In the long-term, all TBI patients who were in VS at discharge either had deceased or recovered into an extreme severe disabled state. Eleven patients were severely disabled, 13 were moderately disabled, and 4 patients were mildly disabled.
Conclusions
More patients than expected recovered to consciousness. Three recovery patterns could be identified in an early phase after starting EINP, making it possible to predict the long-term level of disability.

Key words

Children
Level of consciousness
Long-term outcome
Minimally Conscious State
Vegetative State

Introduction

Recovery to consciousness of young patients who remain unconscious for at least one month after severe brain injury is uncertain[20]. In 1994 the Multi-society task force on the persistent vegetative state (MSTF) calculated, based on earlier outcome research, recovery percentages between 13% (in children with non-traumatic brain injury, nTBI) and 62% (in children with traumatic brain injury, TBI) at 12 months after injury[24,25]. Since then, no comparable studies have been executed, so these percentages are still the prevailing standards in clinical settings as well as in research[16]. However, since then thinking about the vegetative state (VS) has changed dramatically. Especially the introduction of the low-awareness state in 1996 by the International Working Party on the management of the vegetative state[1] and of the Minimally Conscious State (MCS) in 1997 by the Aspen Workgroup on the vegetative and minimally conscious states[17] have changed the ideas about the existence of different levels of consciousness, especially in the post-acute phase. One of the key issues in measuring recovery and in predicting outcome nowadays is to distinguish between these different levels of consciousness. There is however still not a unique and well accepted definition of VS and MCS[10].

In addition to problems in the assessment of recovery to consciousness, it is still unclear whether any treatment in the post-acute phase can contribute to recovery of consciousness. In a review on the current research and consensus on rehabilitation for patients in VS and MCS, Elliott and Walker[15] sum up some arguments to consider early therapeutic interventions: the human brain shows more plasticity than ever thought; studies have shown that a larger population of patients recovered than expected; early interventions have been associated with better outcomes in severe brain injured patients; and intensive specialist rehabilitation programmes have been shown to be effective for the patient and to be cost-effective in the long term. Andrews stated that the rehabilitation of persons with profound brain damage requires the skills of a true interdisciplinary team[2]. Nevertheless, the ultimate evidence for the effectiveness of rehabilitation versus no treatment is lacking[15].

In outcome studies, first the level of consciousness is to be measured, but eventually the long-term functional status is the most important to investigate, as this is strongly related to experienced quality of life and to healthcare costs[4,24]. Of equal importance is the question whether it is possible to identify in an early stage which level of recovery can be achieved in vegetative or minimally conscious patients in order to facilitate appropriate and timely referrals to specialist rehabilitation units[27]. Aspects to be studied as possible predictors of early recovery and of long-term functional recovery are the initial Glasgow Coma Scale score[27,28], the time spent in the Intensive Care Unit as an indication of the severity of the injuries (i.e. dependency of chronic care devices such as ventilation, tracheostomy, intravenal application of medication)[22], and the level of consciousness at different moments.

Course of recovery

Since 1987 an early intensive neurorehabilitation programme (EINP) for children and young adults in a prolonged vegetative or minimally conscious state after severe brain injury is provided in the Netherlands[12,14].
As part of a larger study into the possible effectiveness of EINP, the level of consciousness was studied during the rehabilitation process, as well as the long-term level of disability, giving rise to the following research questions:

- What is the course of recovery for the level of consciousness during EINP?
- Can recovery of consciousness be predicted by any of the studied variables?
- What is the long-term level of disability of the TBI patients?
- Can the level of long term disability of the TBI patients be predicted?

Methods

Patients

The subjects in this study were all patients (n=44), consecutively admitted to the Early Intensive Neurorehabilitation Programme (EINP) between January 2001 and September 2003. Inclusion criteria for admission were age at injury 0-25 years, within 6 months after injury, and Post-Acute Level Of Consciousness scale (PALOC-s) score at admission (Pa) ≤ 6. Because of the heterogeneity in the small group of just 12 nTBI-patients and because of the comparability with other studies, the long-term outcome study is restricted to the TBI-patients (N-32).

Procedures

This study was executed according to a one-group repeated measures design. Within one week after registration to EINP, and successively every two weeks until admission to EINP, patients were examined in the hospital by the first author. Sometimes, the time between registration and admission to EINP was too short to be able to visit the patients in the hospital. The examination procedure was executed along the protocol of the Western Neuro Sensory Stimulation Profile (WNSSP), which was developed in order to examine severe impaired brain injured patients with diminished consciousness [3]. In this protocol a range of structured sensory stimulations are given and simple questions are asked.
Two or three days after admission to EINP, the examination was again executed and repeated every two weeks until discharge from EINP. This examination took place in a quiet room with a constant temperature (23 ± 1°C), always at the same time of day (3:00 p.m.), immediately following the afternoon resting period. Depending on their condition, patients were examined, either sitting in an upright position in a bed or sitting in a wheelchair. At the end of each examination, the outcome scales (PALOC-s and Disability Rating Scale, DRS) were scored.
Additionally, data about demographic variables and relevant clinical features (iGCS = initial Glasgow Coma Scale score[28], length of stay at the Intensive Care Unit, ICU) were collected from the referring hospitals and the families.
Of all TBI patients, the long-term level of functioning was derived by means of a structured interview by telephone with one of the nearest family members (usually

a parent), in which the Disability Rating Scale (DRS) was administered. This was performed by a physiatrist who was blinded for any information about the patients, except the name, gender and age

Measures

Post-Acute Level of Consciousness scale (PALOC-s)

Assessment of the level of consciousness was conducted by using the Post-Acute Level of Consciousness scale (PALOC-s), which was developed and examined as part of the research project. The PALOC-s appeared to be reliable and valid[13]. In the PALOC-s, eight hierarchal levels were distinguished: Coma (P1), VS hypo-reactive (P2), VS reflexive (P3), VS high (re-)active (P4), MCS transitional state (P5), MCS inappropriate (P6), MCS appropriate (P7), and Consciousness (P8), giving rise to scores ranging from 1-8. Each level was illustrated with three to four short descriptive sentences (see Appendix 2).

Disability Rating Scale (DRS)

The Disability Rating Scale (DRS) was used as a measure to establish the global level of disability during EINP as well as in the long-term. The DRS is developed for quantitatively assessing the disability of patients with severe brain injury[26]. It ranges from coma to participation in the community. The DRS consists of eight items and results in a score from 0 (no disability) to 29 (extremely vegetative). A score of 30 is given in outcome research when a patient has died.

The DRS has been recommended as one of the most appropriate instruments in assessing the (long-term) outcome of severely brain injured patients[8,12,26]. To differentiate in this article between the DRS-scores collected together with the PALOC-s during EINP and the DRS-scores collected from the TBI patients in the long-term, the latter will further be named as 'DRS long-term'.

Analyses

To be able to compare the DRS long-term scores with earlier research results, the raw scores on the DRS were transformed into eight category scores[12]. The possibility of categorization was already proposed in the first publication of the DRS by Rappaport et al[26], and found to be as almost as reliable as when the raw scores were used[19].

Data were analysed with the Statistical Package for the Social Sciences (SPSS 11.5.0 and SPSS 14.0, ©SPSS Inc.)

Descriptive statistics such as frequency tables were used to describe the population and the outcome scores. Associations between categorical variables were tested by chi-square test or the Mann-Whitney U test, and group differences were tested by analysis of variance. Distribution plots were used to present scores graphically. Correlation coefficients were calculated by means of the Spearman-r correlation coefficient, due to the limited number of TBI patients.

The multilevel regression analyses were carried out by using the MIXED procedure from SPSS 14.0. For both the PALOC-s as the DRS a multilevel regression analysis was carried out in which Gender, Age, Cause of injury, Treatment, and Time since discharge from Intensive Care Unit were used as explanatory variables. Cause of injury was defined as 'TBI' versus 'nTBI', and Treatment was defined as 'not yet

admitted to EINP' (with inclusion of the first measurement at two or three days after admission) versus 'participating in EINP', hereby differentiating between patients scores before and during the rehabilitation programme. The regression coefficients of Gender, Age, Cause and Treatment were treated as fixed effects, but the coefficient of Time as well as the constant regression coefficient were treated as random effects. A random constant regression coefficient allows the consecutive measurements of the dependent variable on the same individual to be correlated. The random regression coefficient of Time, on the other hand, allows the development of the dependent variable over time to be subject-specific.

Results

Patients

The main characteristics of all consecutively admitted patients to EINP between January 2001 and September 2003 are presented in table 1. Most patients suffered traumatic brain injury (n=32, 73%). All but two patients suffered severe brain injury. The mean initial GCS at hospital admission was 4.8. One patient, who suffered from encephalitis, had an initial GCS of 9, and one patient who suffered from a medulloblastoma had an initial GCS score of 14, although, after surgery she was in a coma and at discharge from the hospital she was minimally conscious. Of 5 nTBI patients the initial GCS was unknown.

The mean age of the patients at the time of injury was 16.0 years (median = 18.1 years, range 1.6-25.5). There was a significant difference in age between the TBI patients (mean age = 18.4 years) and nTBI patients (mean age = 9.4 years) (Mann-Whitney U = 64.0; p=0.00). Of all patients, 28 (63.6%) were males. All but two patients were admitted to EINP within 6 months after injury (median = 2.1 months; range = 0.8–6.6). Patients were discharged from EINP when they did regain consciousness according to rehabilitation team or when in a period of 4 to 6 weeks, no further recovery of the level of consciousness was observed.

Table 1. Demographic characteristics

	Traumatic injury		**Non-traumatic injury**
Total	32[2]	Total	12
Traffic	30 (94)	Cardiac arrest	2 (17)
Other	2 (6)	Near-drowning	3 (25)
		Stroke	3 (25)
		Other	4 (33)
Age at admission to EINP			
0-5 years	2 (6)		5 (42)
6-10	2 (6)		2 (17)
11-15	2 (6)		3 (25)
16-20	13 (41)		1 (8)
21-25	13 (41)		1 (8)
Mean (SD)	18.4 years (6.1)		9.4 years (6.9)
Gender			
Male / Female	21 / 11 (66 / 34)		7 / 5 (58 / 42)
GCS[3] at hospital admission			
Mean (SD)	4.5 (1.3)		4.3 (1.3)
Unknown	0		8 (67)
Length of stay ICU[4] in days			
Mean (SD)	33 (26.7)		20 (18.0)
Unknown	0		1
LOC[5] at admission to EINP			
Vegetative state	24 (75)		9 (75)
Minimally conscious state	8 (25)		3 (25)
Time between injury and admission to EINP in days			
Mean (range)	74 (23 – 198)		61 (38 – 102)
Length of stay in EINP in days			
Mean (range)	109 (26 – 195)		81 (42 – 140)

[2] Numbers and (between brackets) the column percentages within each category, except for the Mean, SD and range scores
[3] GCS = initial Glasgow Coma Scale score at time of injury
[4] ICU = Intensive Care Unit
[5] LOC = Level of consciousness

Course of recovery

Level of consciousness

As can be seen in figure 1, the distribution of PALOC-s scores at discharge resembles a U-shape. Most of the patients (54.5%) recover to PALOC-s level 7 (consistent minimally consciousness) or 8 (consciousness). Almost a quarter (22.7%) of the patients remain extremely vegetative (PALOC-s level 2), and almost another quarter (22.7%) are distributed among categories P3 to P6 of the PALOC-s. The pattern (U-shape) is elicited by the TBI-patients only. The outcome in the nTBI group is more or less equally distributed among the categories of the PALOC-s.

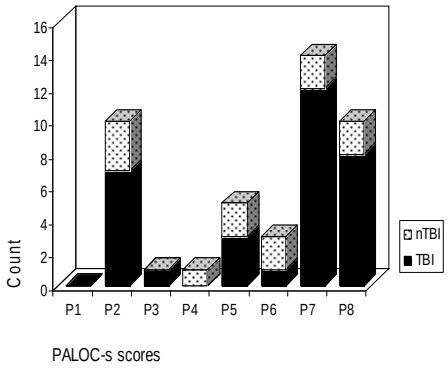

Figure 1. Distribution of the PALOC-s scores of the two subgroups (TBI and nTBI) at discharge from EINP.

Table 2 shows the distribution of the scores on the PALOC-s at discharge (Pd#), related to the scores at admission (Pa#). There were no significant differences in outcome between the TBI-patients and the n-TBI patients ($Z=-1.13$, $p=0.26$), related to the initial PALOC-s score at admission. As can be seen in table 2, all TBI patients who scored P4 or higher on the PALOC-s at admission, recovered to PALOC-s level P7 or P8. In the n-TBI group, the only patient who scored P4 on the PALOC-s at admission did not reach PALOC-s level P7 or P8, because of an unstable neurological condition due to a brain tumour. Of the 22 TBI patients who had a PALOC-s score of P3 or less at admission, 10 recovered to PALOC-s level P7 or P8. Of the eight n-TBI patients with a PALOC-s score of P3 or less at admission, only 1 reached PALOC-s level P7.

Recovery course

To determine the course of recovery, the recovery rates were examined. Figure 2 shows three different courses of recovery. First, we identified all patients who remained in a vegetative state (Remaining vegetative). This was the case in 12 of the 44 patients. Secondly, we identified all patients who were discharged before the 12th week after admission (Fast recovery of consciousness), at which time in EINP the regular evaluation of the progress is scheduled. This was the case in 11 of the 44 patients. All but one of these patients recovered relatively quickly to consciousness or to a consistent minimally conscious level, and were discharged to a regular rehabilitation programme. Lastly, all other patients (Slow recovery to consciousness, 21 of the 44) showed in general a slow recovery rate, and some of them remained in a minimally conscious state (PALOC-s level P5 or P6), not sufficient for further rehabilitation. It can be seen that in this group, the lowest PALOC-s score quickly rose between measurement 8 (8 weeks after admission)

and measurement 10 (12 weeks after admission). The number of patients with low PALOC-s scores in this 'Slow recovery to consciousness' group diminished quickly after the start of EINP: 7 of the 20 patients were scored at level P2 during admission, compared to 3 of the 21 patients at 6 weeks after admission. Figure 2 further shows that the three groups in general differed in the mean PALOC-s score at admission.

The 'Remaining vegetative' group had a mean PALOC-s score of 2.2 (range 1-3), the 'Slow recovery to consciousness' group had a mean PALOC-s score of 3.2 (range 2-6) and the 'Fast recovery to consciousness' group had a mean PALOC-s score of 4.2 (range 2-6) at admission. The PALOC-s scores at admission differ significantly between the three groups ($\chi^2=9.86$, $p=0.00$).

Table 2. Distribution of the number of PALOC-s scores at discharge (Pd#), related to the PALOC-s scores at admission (Pa#), in TBI (n= 32) and nTBI (n=12) groups separately.

TBI	Pd1	Pd2	Pd3	Pd4	Pd5	Pd6	Pd7	Pd8	*Total*
Pa1		2							*2*
Pa2		3	1		3	1	3	2	*13*
Pa3		2					2	3	*7*
Pa4							2		*2*
Pa5							3	2	*5*
Pa6							2	1	*3*
Total		*7*	*1*		*3*	*1*	*12*	*8*	*32*
nTBI	Pd1	Pd2	Pd3	Pd4	Pd5	Pd6	Pd7	Pd8	*Total*
Pa1									*0*
Pa2		2			1				*3*
Pa3		1		1		2	1		*5*
Pa4					1				*1*
Pa5							1	1	*2*
Pa6								1	*1*
Total		*3*		*1*	*2*	*2*	*2*	*2*	*1*

Course of recovery

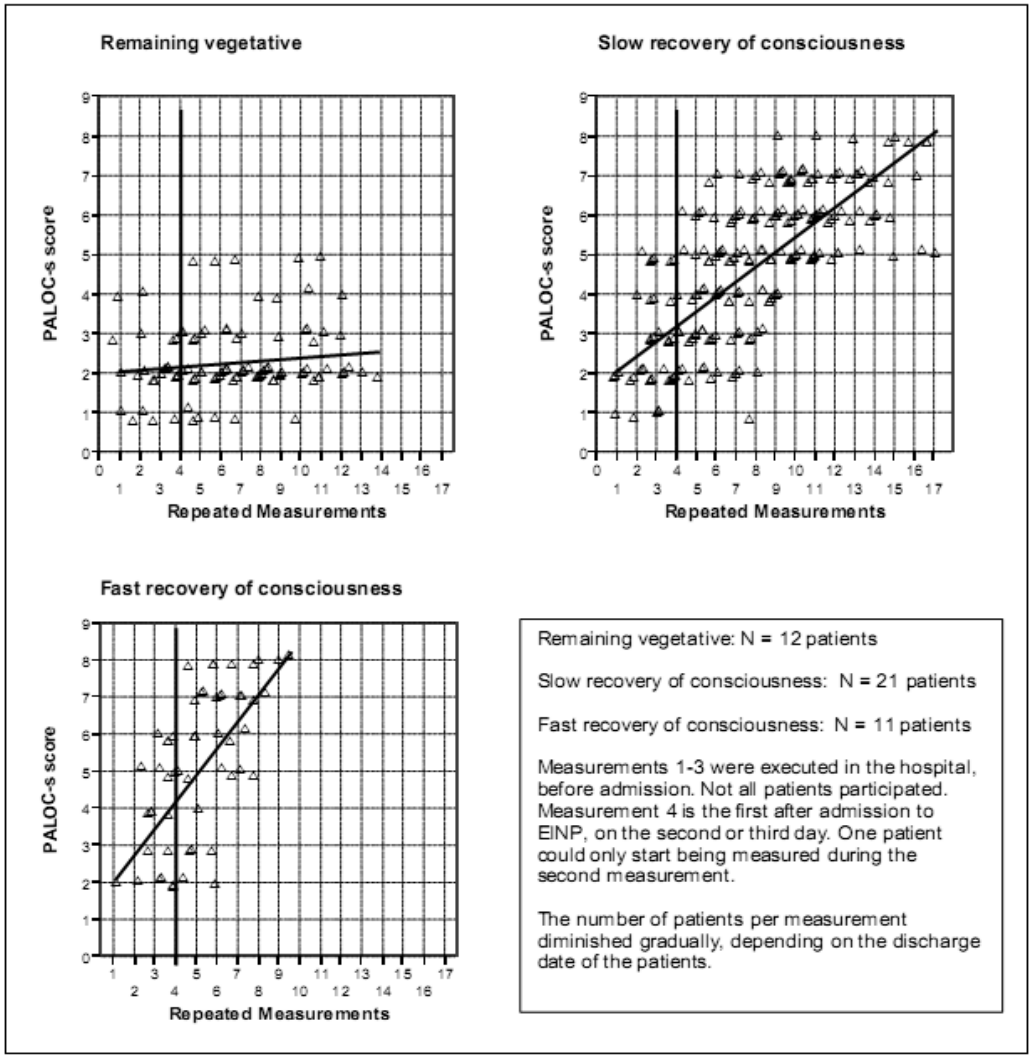

Figure 2. Distributions of the levels of consciousness on the PALOC-s in all measurements, including the linear regressions, in three different outcome groups. Each triangle represents one measurement of one patient.

Prediction of the recovery course during EINP

The results of the multilevel regression analysis (Table 3) show only a positive association between 'Time since discharge from ICU' and the PALOC-s scores, indicating that recovery to consciousness increases with time. None of the other

explanatory variables (Gender, Age, Cause and Treatment) had any significant predictive effect. The standard deviation of the random intercept distribution was 1.35, and that of the distribution of the random coefficient of time was 0.02. Both values were significantly different from zero ($p<0.001$), indicating that strong inter-individual differences exist with respect to the time course of the PALOC-s.

Table 3. Estimates of fixed effects from the multilevel analysis for PALOC-s (N=44)

	BE	Se	T
Gender	0.09	0.47	0.20
Age	0.06	0.04	1.68
Cause	0.57	0.60	0.95
Treatment	0.28	0.14	1.60
Time	0.03	0.00	7.07***

*** $p<0.001$

The results presented in Table 4 show that also the DRS scores during EINP decrease significantly over time. Again, none of the other explanatory variables had any significant predictive effect.

Table 4. Estimates of fixed effects from the multilevel analysis for DRS (N=44)

	BE	Se	T
Gender	-0.21	0.94	-0.22
Age	-0.10	0.07	-1.39
Cause	-0.55	1.19	-0.46
Treatment	-0.42	0.35	-1.22
Time	-0.07	0.01	-6.32***

*** $p<0.001$

The standard deviation of the random intercept distribution was 2.41, and that of the distribution of the random coefficient of time was 0.06. Both values were significantly different from zero ($p<0.001$), indicating that strong inter-individual differences exist with respect to the time course of the DRS.

Long-term functioning

The long-term outcome of the TBI-patients is determined between 2.0 and 4.4 years after discharge (mean = 3.1 years).
The results show a peak of 13 patients at level 6 of the DRS long-term, which can be defined as moderately disabled.18 The other 19 patients are more or less equally distributed among five of the other categories (see Figure 3). No scores were obtained in the categories 'vegetative' and 'no disability'. Of the seven patients who were in VS at discharge, four have since deceased. The remaining three patients are considered extremely severe disabled.

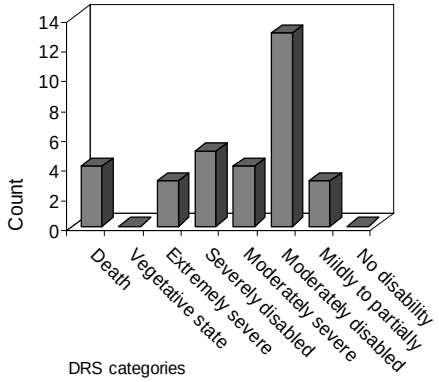

Figure 3. Frequencies of the DRS long-term category scores of the TBI group (N = 32)

To investigate whether the long-term level of functioning can be predicted in an early stage, the raw scores on the DRS long-term were correlated with the initial Glasgow Coma Scale scores (iGCS) and the length of stay in the ICU (as indicators of injury severity), with the age at injury, and with the levels of consciousness at EINP admission and discharge as determined by means of the PALOC-s. Table 5 shows that only the last two parameters correlate significantly with the long-term scores on the DRS.

Table 5. Spearman correlation coefficients between five variables and DRS long-term raw scores in TBI patients only (N=32)

	Correlation	p-value
Initial GCS	- 0.21	0.25
Length of stay ICU	0.28	0.17
Age	- 0.21	0.25
PALOC-s admission	- 0.51	0.00
PALOC-s discharge	- 0.79	0.00

Discussion

The aim of this study was twofold. Firstly, the course of recovery and the long-term level of independency were investigated of young patients who remained unconscious for at least one month and at most six months after severe brain injury. Secondly, the factors which could predict recovery in an early stage were investigated.

The results lead to the following conclusions.

Recovery

The number of patients that recovered to consciousness is higher than expected, considering the severity of the injuries and the duration of the unconscious state. Three-quarters of the patients were in VS at admission, generally more than two months after injury. At discharge, two-thirds of the patients were conscious and could be admitted into a regular rehabilitation programme. Boyer and Edwards, describing a similar treatment programme for children and adolescents with TBI, found that of 83 patients who were in VS after 3 months, 43% were still in VS after one year[7]. In this study of 24 TBI patients, 33% remained in VS. Recovery in nTBI patients is less favourable, as could be expected based on the calculated chances for recovery by the Multi-Society Task Force[25]. In this study, one-third of all nTBI patients regained consciousness, one-third remained in VS and one-third were in MCS at discharge.

On the long-term (2 to 5 years after injury) the majority of the TBI patients (16 out of the 28 surviving patients, 57%) were able to function, at least partly, in an independent way. Also this percentage score is relatively high, compared to the study of Boyer and Edwards, who found that 27-43% of their patients achieved independence in the activities of daily living[7]. Furthermore, it is of importance to note that 60% of all patients who remained in VS, died within a few years. The remaining patients showed some recovery to a state of extremely severe

disability. It seems needless to be afraid of long surviving patients, whose vegetative state causes sometimes a great burden on their relatives lives, as sometimes is expressed in publications about ethical aspects of the treatment of patients in an unconscious state[11].

Prediction of recovery

Concerning the research question, which factors can predict recovery, the following conclusions can be drawn.

Firstly, neither age, gender, the initial Glasgow Coma Scale score, nor the length of stay at the ICU can predict recovery. So, whenever a patient ultimately moves over from coma into VS, no prediction can be made about recovery, based on these aspects, The multilevel regression analyses only showed a relation between time since discharge from the ICU and the level of consciousness, reflecting a gradual improvement, rather than a sudden change of the level of consciousness. It is not clear whether this is a reflection of spontaneous recovery[21] or is triggered by the treatment given. No relation, however, was found between the recovery rate before and after starting EINP.

Secondly, more promising for prediction of recovery is the level of consciousness as measured by the PALOC-s. Of all admitted patients, about one-quarter showed a relatively quick recovery to consciousness and about half of the patients showed only gradual recovery. In a repeated measurement design, the probability of recovery of consciousness could be established in an early phase. All patients who scored level P4 (VS high [re-]active) or better on the PALOC-s recovered ultimately to consciousness. Almost all patients who initially scored P2 (VS hypo-reactive) or P3 (VS reflexive) on the PALOC-s, and ultimately recovered a higher level of consciousness, showed some recovery within 6 weeks after admission to EINP. Therefore, the PALOC-s is an important tool in predicting recovery of consciousness, as well as in measuring progress over time during the rehabilitation programme.

The long-term level of functioning was only significantly correlated with the observed level of consciousness at admission as well as at discharge from EINP. No other variable correlated with the long-term DRS scores. This result underlines the importance of the PALOC-s as a clinical tool in predicting the long-term level of disability.

As far as we know, this is the first study in which the recovery process in a substantial number of patients was measured in a systematic manner, before, during and after the application of an early intensive neurorehabilitation programme. As Whyte stated recently, such a programme should be based on well established theories[31]. The underlying theories of EINP can be summed up by three basic principles. Firstly, the plasticity of the brain is an important biological phenomenon, which is of great adaptive significance in healthy brains as well as in injured ones[29]. Secondly, recovery processes start as early as from the moment of injury and can last long, even many years, based on a range of different neural mechanisms[5,6]. And thirdly, the brain is highly sensitive to external and internal sensations and

responds to it by rewiring, changing of (sensory) representations, reorganization and newgrowth of neurons, dendrites and axons in order to adapt in the best way possible to what is needed[5,9,23]. Although we did not find a correlation between the application of EINP and the level of consciousness, the percentage of recovery to consciousness, especially in the TBI-group, was reasonably high.

Limitations

An important limitation in this study is the size of the studied group, related to the variability in the cause of injury and with the age range. This resulted in a heterogeneously composed study group. It can further be questioned whether all discriminating variables are incorporated in this study. This is probably not the case[30]. Variables as premorbid functioning, type and size of injuries, initial treatment provided in the ICU, or influence of close relatives on recovery are not included in the study due to extreme methodological difficulties. Therefore, there is a chance that the prediction of recovery can be improved by incorporating other variables. However, we do not consider this as very plausible, as we did choose the most important variables generally used in outcome research. Although the studied group is relatively small, the results are nevertheless important. Not only results regarding prediction of recovery for this type of patient but also regarding the importance of the application of an early intensive rehabilitation programme.

Another possible limitation in this study is the use of the PALOC-s. The scale is developed as part of the wider research project of EINP and appeared to be highly reliable and to have a good level of validity[13]. Replication of these results is needed, before further certainty can be achieved about the reliability and validity of the PALOC-s. In the meantime however, this scale can be of great value in the difficult but important process of differential diagnosis between the vegetative and the minimally conscious state, as recently stated by Gill-Thwaites[18]. This conclusion is strengthened by the possible predictive value of the PALOC-s for long-term (in-)dependency. This being possibly very helpful in clearly defining the rehabilitation process for a patient.

We tried to compare the rate of recovery before starting EINP and after starting, by using the scores on the PALOC-s as determined during the repeated measurements. This process was hindered by the fact that most of the patients had small numbers of pre-treatment measurements: 10 of the 44 patients participated only once, 19 patients participated twice, 6 patients participated three times and only 9 patients participated four times. This resulted in102 pre-treatment measurements, compared to 288 measurements during the application of EINP (M=6.5 per patient, range 1-13). In further effect research, it is of great importance to collect more data of all patients before starting treatment.

The conclusions of this study are only valid for severely injured patients. By nature of

this study, in which a programme meant for severe injured patients was investigated, no moderately or mildly injured patients were included.

Conclusions

As far as we know, this is the first study ever in which the course of recovery in a cohort of children and young adults in prolonged VS or MCS after severe brain injury is investigated in such a systematic manner. More patients than expected recovered to consciousness. Moreover, in an early phase after admission to EINP, three patterns of recovery could be identified, making it possible to predict whether recovery to consciousness would occur, within two to three weeks in almost half of the cohort and within 6 weeks in almost all other patients. These results can play an important role in clinical decision-making and are of great importance for further research.

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CHAPTER 6

Children and young adults in a prolonged unconscious state after severe brain injury: long-term functional outcome as measured by the DRS and the GOSE after early intensive neurorehabilitation

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Abstract

Objective
To investigate the long-term (2-15 years) functional outcome of children and young adults who received an early intensive neurorehabilitation programme (EINP) after a prolonged period of unconsciousness due to severe brain injury; to differentiate between traumatic brain injury (TBI) and non-traumatic brain injury (nTBI); and to compare the results on two different outcome scales: the Disability Rating Scale (DRS) and the Glasgow Outcome Scale Extended (GOSE).

Subjects
145 patients, who were admitted to EINP between December 1987 and January 2001.

Outcome measures
The Post-Acute Level of Consciousness scale (PALOC-s), the DRS, including categorized scores (DRScat), and the GOSE.

Results
The long-term functional level of 90 patients could be determined, of whom 25 were deceased. The mean DRS-score of the surviving patients was 6.8 (SD=6.6); the mean score on the GOSE was 4.5 (SD=1.7). There was a significant difference in the outcome amongst traumatic and non-traumatic patients ($t(88)=4.21$; $p<0.01$). The correlation between the DRS and the GOSE was high (Spearman rho = 0.85; $p<0.01$), as well as the correlation between the categorized scores of the DRS and the GOSE (Spearman rho = 0.81; $p<0.01$). The distribution of outcome scores on the DRScat is more diverse than on the GOSE. Especially item 7 of the DRS, measuring functional independence, showed considerable variance in discriminating between different outcome levels.

Conclusions
More patients with TBI than expected reached a (semi-) independent level of functioning, indicating a possible effect of EINP. Patients suffering from nTBI did not demonstrate these outcome levels.
Only a few patients stayed in vegetative state for more than a couple of years.
In this cohort of severe brain injured young people, the DRS offered the best investigative possibilities for long-term level of functioning.

Keywords

Consciousness
Children
Functional recovery
Long-term functioning
Minimally conscious state
Rehabilitation
Severe brain injury
Vegetative state
Youngsters

Introduction

Severe brain injury in young people, with a prolonged period of unconsciousness of several weeks or months, results in an extensive loss of function regarding almost all capabilities. This usually leads to a decreased level of independence, and results in the majority of cases in a lower level of social participation[9]. A number of patients do not regain consciousness and continue to remain in a vegetative state (VS) or minimally conscious state (MCS) for many years, even resulting in death for some patients[24]. For those children remaining in a vegetative state three months after suffering severe traumatic brain injury, the probability of remaining in a vegetative state for at least one year was calculated by the Multi-Society Task Force on Persistent Vegetative State (MSTF) for 30% (CI99 = 13-47) and the probability of death was calculated for 14% (CI99 = 1-27)[25]. For children who suffered a non-traumatic brain injury the probability of remaining in a vegetative state was calculated for 97% (CI99 = 89-100) and the probability of death was calculated for 3% (CI99 = 0-11).
Since the 1960's treatment programmes have been developed, focusing on the recovery of consciousness and on an early start of recovery of functions in non-responsive patients[4,7]. The different programmes vary considerably in terms of content, target group, intensity, duration, location, and finances[29,30]. It is extremely difficult to investigate the effects of these rehabilitation programmes because of a range of methodological difficulties, a lack of sound treatment theories[37] and ethical limitations[10]. As a result, the efficacy of these kind of programmes has remained unproven[21]. A few studies, however, do support the beneficial effects of early intensive neurorehabilitation of non-responding patients[11,28]. Earlier investigations[12,27] show that only one quarter of patients who were still in VS or MCS one month after injury regain self-care independency, implying that three quarters of the patients require aid from either family members or a health care facility. Patients who remained dependent and who required a full-time care facility often expressed their anguish and demonstrate a low level of experienced quality of life[22]. The close relatives of these patients are also often distressed, especially when they have to deal with behavioural changes[36]. Therefore, each treatment programme that can contribute to better outcome levels will ultimately reduce emotional problems for both the patient and their family.

In 1987 a comprehensive early intensive neurorehabilitation programme (EINP) for children in VS or MCS was developed at the Rehabilitation Centre Leijpark (RCL) in the Netherlands, aiming at recovery of consciousness and ultimately at ameliorating the level of independence. The outcome upon discharge of 145 patients, aged 0-25 who were admitted between December 1987 and January 2001, showed that 62% of the patients had reached full consciousness, 27% were in MCS, 6% were in VS, and 5% deceased[6]. Most of the conscious patients were discharged to a regular rehabilitation facility, indicating potential for a reasonable recovery of long-term function.

The question remains whether the recovery of function achieved at the time of discharge indeed led to higher levels of independence in long-term functioning. This study therefore focuses on the long-term functional recovery of the patients mentioned above, after receiving EINP. This is the first large-scale Dutch study concerning long-term disability in young patients with severe brain injury and with a known long period of disturbed consciousness.
Other objectives of this study include the comparison of outcome amongst traumatic and non-traumatic patients given that it is to be expected that the latter group has fewer possibilities for recovery than the first[25]. Based on the results a recommendation will be given about the relevance of EINP.
Finally, a comparison of results will be made concerning the two different and widely used outcome measures; the Glasgow Outcomes Scale Extended (GOSE)[17,38], and the Disability Rating Scale (DRS)[26].

Outcome after severe brain injury can be examined at different levels of functioning: neuropsychological functions[19], quality of life[1] or the level of disability[32]. In an overview of some frequently used outcome measures for clinical trials in neurotrauma, Bullock et al.[2] concluded that the Glasgow Outcome Scale (GOS)[16] or its extended form (GOSE), and the DRS are the most widely used outcome measures. They recommend that the GOSE be further evaluated, especially in relation to the higher sensitivity of this instrument for the middle outcome categories. The structured nature of the interview should protect against inter-observer variability. They also concluded that the concordance between the DRS and the GOS is moderate, with an underestimation by the DRS of the severity of outcome related to the GOS. Others however, showed a higher sensitivity of the DRS in the most severe outcome levels. Hall et al.[13] stated in 1985 that "the DRS more sensitively reflects improvement during in-hospital rehabilitation than the GOS, 71% to 33%, respectively" (p35). The latter effect is in all probability a reflection of the sensitivity of the DRS to changes in seriously impaired patients. Therefore, for a population concerning high probability of low outcome (VS or MCS), the DRS seems to be more useful in differentiating between outcome levels. Based on the comparison of these two instruments, a recommendation will be given for examining functional outcome clinically and scientifically in this interesting group of patients.

Method

Patients
Subjects included in this study were all patients (N=145) admitted to the EINP between December 1987 and January 2001. Criteria for admission were: age between 0-25 years, in a vegetative or minimally conscious state subsequent to severe brain injury, admission date between 2 weeks and 6 months after injury.
Admission took place between 0.7-7.6 months (Mean(M)=2.3, Median=2.1, SD=1.2) after injury. One patient was admitted more than a half year after the injury due to a waiting list. Of the 145

patients admitted to the EINP programme, 107 patients suffered severe brain injury, with an initial Glasgow Coma Scale (GCS)[31] score less than or equal to eight. One patient with a GCS-score of 9 was admitted because of the extended vegetative state. For 37 patients the initial GCS-score was unknown.

In Table 1 the most important characteristics of the participants are presented. The cohort is divided into two groups: 104 patients who suffered traumatic brain injury (TBI: 91 of the cases was caused by a traffic accident, 12 caused by a fall, and in 1 case caused by a blow to the head) and 41 patients who suffered a non-traumatic brain injury (n-TBI). In this group different kinds of causes are represented more or less equally: near-drowning (N=11), encephalitis (N=10), cardiac arrest (n=7) and other causes of anoxia (N=10). Three patients suffered a stroke. There are two main differences between the TBI group and the n-TBI group. Firstly, the mean age at time of injury of the n-TBI group is significantly lower ($t(143)=5.74$; $p<0.01$) , and secondly the level of consciousness (LOC) at the time of discharge from EINP is significantly less encouraging in the n-TBI group, as compared to the TBI-group ($t(143)=3.51$; $p<0.01$).

Outcome measures

The PALOC-s is a newly developed observation scale to investigate the level of consciousness in patients with a prolonged loss of consciousness after severe brain injury. The PALOC-s is a one item rating scale including eight levels of consciousness: 1 = coma, 2 = hypo-responsive vegetative state, 3 = reflexive vegetative state, 4 = high (re-)active vegetative state, 5 = transitional minimally conscious state, 6 = inconsistent minimally conscious state, 7 = consistent minimally conscious state, and 8 = conscious state. Preliminary results show that the PALOC-s is reliable ($0.85 < r < 0.94$) and valid ($0.88 < r < 0.93$)[5]. In this study, the scores on the PALOC-s were reduced to class scores: coma (PALOC-s score of 1), vegetative state (VS, PALOC-s score 2-4), minimally conscious state (MCS, PALOC-s score 5-7), and conscious state (CS, PALOC-s score of 8).

The Disability Rating Scale (DRS)[26] consists of eight items, either scored on a four, five or six-point scale. A high score on an item indicates a low level of functioning on that aspect. The scores on the eight DRS items can be summed up to values from 0 to 29. A score of 30 is given when a patient has deceased. The DRS is reliable and valid[14,26] and is able to track a patient from the lowest level of unconsciousness up to independent functioning in the community. The DRS has proven to be sensitive to improvement until at least five years after injury[15], especially in patients who are still (partly) dependent one year after injury. The DRS was translated into Dutch by the first author, in a forward-backward procedure[23], and adapted to be filled out by a proxy of the patient.

Table 1. Demographic characteristics

	Traumatic injury	**Non-traumatic injury**
Total Number	104[1]	41
Age at admission to EINP		
0-5 years	12 (12)	23 (56)
6-10	17 (16)	5 (12)
11-15	25 (24)	5 (12)
16-20	38 (37)	5 (12)
21-25	12 (12)	3 (7)
Mean (SD)	14.8 years (5.8)	8.0 years (7.5)
Gender		
Male / Female	76 / 28 (73 / 27 %)	28 / 13 (68 / 31 %)
GCS[2] at admission to hospital		
Mean (SD)	3.9 (1.9)	3.2 (2.2)
Unknown	20 (19)	17 (42)
LOC at admission to EINP[3]		
Vegetative state	45 (43)	18 (44)
Minimally conscious state	59 (57)	23 (56)
LOC at discharge from EINP		
Deceased	3 (3)	4 (10)
Vegetative state (VS)	4 (4)	5 (12)
Minimally conscious state (MCS)	24 (23)	15 (37)
Conscious state (CS)	73 (70)	17 (42)

[1] Numbers and (between brackets) are the column percentages in each category, except for the Mean and SD scores
[2] GCS = Glasgow Coma Scale score
[3] LOC = Level of consciousness

The GOSE is an extension of the Glasgow Outcome Scale (GOS)[17,38]. The GOSE is a one-item rating scale including eight outcome categories (from 'deceased' to 'upper good recovery', see table 2) and can be administered through a structured interview. Compared to the GOS, the GOSE has proved to be more sensitive to

changes in the mild to moderate range of TBI[34,35]. The GOSE was translated into Dutch in an earlier research programme at the Erasmus University of Rotterdam and was administered in a structured interview with a proxy of the patient, as proposed by Wilson[38].

Procedures

This study was carried out following a one-group archived pretest-posttest design. The local medical ethics committee gave ethical and lawful approval of the study.

The first author, an experienced neuropsychologist, investigated the patients' medical files to collect their demographic and injury-related characteristics, and to determine the level of consciousness (LOC) upon admission and discharge to the EINP. Three possible levels were identified by means of the PALOC-s: vegetative state (VS), minimally conscious state (MCS), and conscious state (CS). The procedure has been previously described in detail[6].

Next, all subjects were contacted in writing and asked for informed consent. When no reaction was received, contact was made by telephone. After having received the informed consent from the patients or their family, an appointment was made for administration of the outcome scales with a proxy of the patients (usually one of the parents). All assessments took place between November 2002 and June 2003 by the second author, a neuropsychology trainee, generally at the rehabilitation centre. Some assessments were done at the patients' home. In one case concerning an emigrated patient, the administration was fully executed in a telephone interview. The assessment was carried out in one session, and completed in 20 to 30 minutes. The GOSE was always administered first.

Statistical analyses

To be able to compare the DRS and the GOSE properly, the scores on the DRS were transformed into category scores. The possibility of categorization was already proposed in the first publication of the DRS by Rappaport et al.[26]. Gouvier found that the inter-rater reliability of this ranked DRS was slightly less than that of the summed score, but still very high (0.95 vs. 0.98 in a study with three raters and 40 patients)[8]. Gouvier concluded that deriving category scores from raw DRS-scores did not result in losing much information, ensuring that the categories represent meaningful levels of recovery in their own right. Therefore, we used this eight-level categorised DRS-scoring method (DRScat, see table 2). To avoid negative correlations, the raw scores were converted to category-scores in the same means as the GOSE: a DRScat-score of 1 reflects the worst outcome category (deceased) and a score of 8 reflects the best outcome category (no disability). This combination of scores on the DRS and GOSE is represented in table 2.

Table 2. Disability Rating Scale category levels (DRScat), as converted from the raw scores of the Disability Rating Scale, and GOSE category levels

Raw DRS score	Categories DRS (DRScat)	Level	GOSE
0	No disability	8	Upper good recovery
1-3	Mildly to partially disabled	7	Lower good recovery
4-6	Moderately disabled	6	Upper moderately disabled
7-11	Moderately severe disabled	5	Lower moderately disabled
12-16	Severely disabled	4	Upper severely disabled
17-21	Extremely severe disabled	3	Lower severely disabled
22-29	Vegetative state	2	Vegetative state
30	Deceased	1	Deceased

The raw scores on the last two items of the DRS were treated individually during the analyses. These two items present most likely the best possibilities to differentiate between the outcome levels. Item seven reflects the "Level of Functioning" on six levels: 0 = completely independent, 1 = independent in a particular environment, 2 = mildly dependent, 3 = moderately dependent, 4 = noticeably dependent, and 5 = totally dependent. Item eight reflects the "Employability" or "Educationability" on four levels: 0 = not restricted (for labour or education), 1 = selected, competitive jobs; or can perform most school tasks on a regular basis, 2 = sheltered, non-competitive workshop; or requires assistance for all school tasks, 3 = not employable; or education is not possible[33].

Data analyses were performed with the Statistical Package for the Social Sciences (SPSS 11.0.1, © SPSS Inc.). Descriptive statistics such as frequency tabulations were used to describe the population and the scores on the scales. Association between variables was established by calculation of the Spearman rho correlation coefficient. Curve fitting was done using polynomial regression models containing first-, second-, and third-order terms. To obtain a quantitative measure of how well these models predicted the dependent variable R^2 was used. Group differences were tested by the t-test or by the χ^2-test.

Results

Participants

Out of the total 145 patients, ninety patients could be included in this study, of which 25 (19% of the TBI group and 48% of the n-TBI group) were deceased. Twelve patients (8%) had moved and could not be located and 43 patients or their families (30%) did not return the informed consent.

Long-term outcome

The time between injury and the determination of the long-term functional outcome varied between 2.4 and 15.7 years (M=7.2, Median=6.7, SD=3.3). The mean age of the surviving patients was18.6 years (range 5-35, SD=6.3), and 71% were male. The main characteristics of the participating patient group (N=65) and the non-participating patient group (N=55) were compared to investigate whether the groups differed (see table 3).

Table 3. Characteristics of the participating and the non-participating groups of patients. Except for the first two variables, all data are with exclusion of the deceased patients.

Variable	**Participating**	**Non-participating**
Number	90	55
Deceased	12 TBI (19%) 13 n-TBI (48%)	n.a.
Gender	70.8% male	72.7% male
TBI / n-TBI	78.5% TBI	74.7% TBI
Age at injury (yrs)	M=12.6, SD=6.2 Range: 0.6-25.0	M=13.3, SD=7.3 Range: 0.7-23.7
Current age (yrs)	M=18.6, SD=6.3	M=19.6, SD=8.6
Level of consciousness at admission	VS=51%, MCS=49%	VS=69%, MCS=31%
Level of consciousness upon discharge	VS=0%, MCS=23%, CS=77%	VS=4%, MCS=25%, CS=71%
Time since injury (yrs)	M=7.5, SD=3.4 Range: 2.4-15.7	M=7.9, SD=3.1 Range: 2.6-13.9

VS = Vegetative State; MCS = Minimally Conscious State, CS = Conscious State

No differences in the two groups were found in age ($t_{(118)}=0.72$; p=0.47), time since injury ($t_{(118)}=0.49$; p=0.63), cause of injury (TBI versus n-TBI) ($\chi^2_{(1)}=0.26$; p=0.61), or gender ($\chi^2_{(1)}=0.06$; p=0.81). Further analysis showed no association between group membership (participating versus non-participating) with level of consciousness at admission (VS or MCS) ($\chi^2_{(1)}=1.45$, $\phi=0.11$, p=0.23), nor with the level of consciousness upon discharge (VS, MCS, or CS) ($\chi^2_{(2)}=2.58$, $\phi=0.15$, p=0.28). Therefore, with regards to different essential aspects related to functional capacities, the studied group was representative for the total population that participated in EINP.

Long-term outcome

The mean DRS-score of the total group, including the deceased (N=90) was 13.4 (SD=11.8). For the surviving group

(N=65) the mean DRS-score was 6.8 (SD=6.6), for the TBI patients (N=51) it was 5.4 (SD=5.3), and for the surviving n-TBI patients (N=14) the score was 12.1 (SD=8.1). The mean GOSE-score of the total group was 3.5 (SD=2.1). For the surviving group (N=65) the mean GOSE-score was 4.5 (SD=1.7), for the TBI patients (N=51) it was 4.9 (SD=1.7), and for the surviving n-TBI patients (N=14) the score was 3.3 (SD=0.9).

Table 4 shows the distribution of the scores on the DRScat and on the GOSE. There was a significant difference between the TBI and the n-TBI patients on both the DSRcat ($t_{(88)}$=4.36; p<0.01) and the GOSE ($t_{(88)}$ = 4.37; p<0.01). The TBI group, with 83.3% of the cases in the upper three categories of the DRScat, scored clearly better compared to the n-TBI group (only 42.9% in the upper three categories).

Table 4. DRScat scores and GOSE scores of the surviving patients (N=65), individually for the traumatic patients (TBI) and for the non-traumatic patients (n-TBI) presented in number and in percentages per column.

Level	DRScat		GOSE	
	TBI	**n-TBI**	**TBI**	**n-TBI**
8	6 (11.7%)	0	3 (5.9%)	0
7	15 (29.4%)	2 (14.3%)	12 (23.5%)	0
6	21 (41.2%)	4 (28.6%)	4 (7.8%)	0
5	1 (2.0%)	1 (7.1%)	4 (7.8%)	1 (7.1%)
4	5 (9.8%)	1 (7.1%)	3 (5.9%)	1 (7.1%)
3	2 (3.9%)	4 (28.6%)	25 (49.0%)	8 (57.1%)
2	1 (2.0%)	2 (14.3%)	0	4 (28.6%)
Total	**51 (100%)**	**14 (100%)**	**51 (100%)**	**14 (100%)**

Comparison between scores on the DRS and GOSE

The distribution of the scores over the categories differed between the GOSE and the DRScat. On the DRS the majority of the patients scored in the upper three levels, whereas on the GOSE the majority of the patients scored in the lower three levels, especially in level 3.

The correlation between the DRS and the GOSE was high (Spearman rho=0.84; p<0.01), as well as the correlation between the DRScat and the GOSE (Spearman rho=0.81; p<0.01).

As figure 1 shows, the scores on the DRScat seemed to be more differentiated in the lower levels of functioning, whereas the GOSE-scores were more differentiated

in the upper levels of functioning. Level 6 (containing 25 patients) and level 7 (containing 17 patients) of the DRS were differentiated in six GOSE levels, and in return, level 3 (containing 33 patients) of the GOSE was differentiated in six DRS levels. Although there was a clear linear trend in the data ($R^2 = 0.47$), a cubic curve fitted the data better ($R^2 = 0.58$; test for significance of the difference: $F(2,61) = 6.14$, $p = 0.00$).

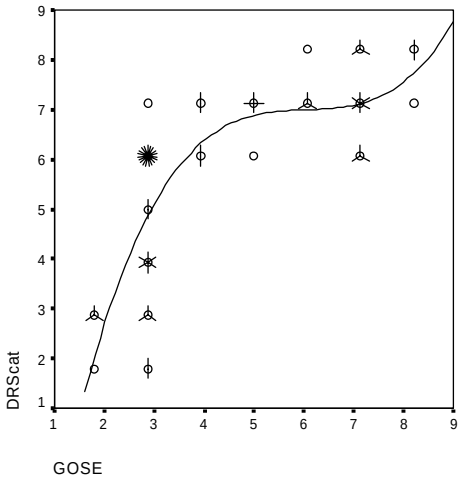

Figure 1. Scatter plot of the scores on the GOSE and on the DRScat, with a cubic curve fitted to the data. An open dot represents 1 case, the number of lines connected to the other dots represents the total number of cases.

Functionality and employability / educationability

The scores on the two separate items of the DRS concerning functionality (item 7) and employability / educationability (item 8) showed considerable variations. In particular, the variance on item 7 in the TBI group was high (see table 5). The scores were more or less equally distributed among the six categories, showing that one third of the TBI patients were moderately independent, one third were mildly or moderately dependent and one third were noticeably or totally dependent. A majority of 64% of the n-TBI patients was noticeably or totally dependent.

Table 5. Distribution of the traumatic (TBI) and the non-traumatic (n-TBI) patients on Item 7 (functionality) of the DRS

Level	**TBI**	**n-TBI**
Completely independent	13 (25.5%)	1 (7.1%)
Independent in a particular environment	4 (7.8%)	0
Mildly dependent	9 (17.6%)	1 (7.1%)
Moderately dependent	8 (15.7%)	3 (21.4%)
Noticeably dependent	8 (15.7%)	2 (14.3%)
Totally dependent	9 (17.6%)	7 (50%)
Total	**51 (100%)**	**14 (100%)**

Table 6 shows the distribution of the scores for both groups among the four levels of the employability item 8 of the DRS, indicating that almost half of the surviving TBI group was able to participate in work or school activities, compared to one quarter of the n-TBI group.

Table 6. Distribution of the traumatic (TBI) and the non-traumatic (n-TBI) patients on Item 8 (employability/educationability) of the DRS

Level	TBI	n-TBI
Not restricted	6 (11.8%)	0
Selected competitive jobs / can perform most school tasks on a regular basis	16 (31.4%)	4 (28.6%)
Sheltered non-competitive workshop / requires assistance for all school tasks	22 (43.1%)	4 (28.6%)
Not employable / education is not possible	7 (13.7%)	6 (42,9%)
Total	**51 (100%)**	**14 (100%)**

Discussion

This study describes the long-term outcome of children and young adults with severe brain injury who had been in a vegetative state or a minimally conscious state for a considerable period. The results showed that, though full recovery is rare, the majority of patients eventually reached a (semi-) independent level of functioning. For the patients with traumatic brain injury 37% (GOSE) to 82% (DRS) recovered to partly or total independency. Forty-three percent were able to perform substantial work or accomplish most or even all school tasks without help. No TBI-patients seemed to be in VS several years after injury. When we compare the results of this study to the results of our discharge study concerning the same population[6], we can conclude that almost all the patients who were in a vegetative state upon discharge from EINP deceased in the period following release. Also, approximately one quarter of the patients in MCS deceased. It can be assumed that most of them were in the lowest level of the MCS, the transitional state. Eventually almost 50% of the n-TBI patients deceased, compared to 12% of the TBI patients. The more encouraging outcome of TBI patients is in full accordance with other outcome studies[25], and with our expectations. Furthermore, one can conclude that patients who are still in VS 12 months after injury are likely to die within a couple of years.

It is not possible to compare our data in detail to those of earlier studies due to, for example, differences in study design and sample characteristics. To assess the effect of a treatment programme like EINP, a controlled group study design is needed. Nevertheless, some of the results of this study suggest that more TBI-patients than presumed recovered to a reasonable level of independence, as can be seen when comparing the results with earlier outcome studies. Firstly, at admission to EINP none of the patients had an indication for rehabilitation with a poor prognosis for substantial recovery, however eventually 50-67% of all traumatic patients reached a level of at least partial independence. Of

the 25 patients who were in VS for three months or more, 11 (44%) reached this level. This is substantially more than described by Kriel et al.[18]. They studied a cohort of 188 young patients (0-20 years) who suffered a severe brain injury, of whom 60 were in VS for more than 90 days. Kriel et al. found that 1-20 years (Median = 8 years) after trauma, only 10% of the patients were verbal communicators and 30% had reached some level of motor independency. Secondly, comparing the results of this study with the earlier mentioned calculations of recovery probability made by the Multi-Society Task Force (MSTF)[24,25], and with the results of the study of Groswasser and Sazbon[12,27], in our study the long-term outcome of patients who suffered a traumatic brain injury seems to be more encouraging, therefore indicating possible therapeutic effects of the early intensive neurorehabilitation programme. The MSTF calculated a probability of 30% remaining in a vegetative state with an estimated survival of 7.4 years (±1.8) for children 7 to 18 years old[25]. In our study none of the TBI-patients were in a vegetative state within one year of the injury. Groswasser and Sazbon found that 11% of patients who were unconscious for more than one month were able to resume working in the open job market and 49% were engaged in sheltered non-competitive workshops[12]. In this study these percentages were respectively 43 and 43. In this study, half of the patients were classified in the 'lower severe disability' category of the GOSE, mainly because they needed some kind of physical help during daily life. In scoring the GOSE it is not possible to take into account the level of mental independence. As it is generally accepted nowadays that social participation is a function of mental capacities rather than of physical capacities, it seems worthwhile to use other measures for the classification of the level of disability. In this study especially item 7 of the DRS, which requests functional independency, showed a substantial variation in the scores. Demonstrating that in the studied population, the level of functioning is more diverse than the results of the GOSE suggested. The use of the DRS as a whole, and item 7 especially, can contribute to a better insight in the need for different kinds of specialized facilities and care. This is in accordance with the latest views regarding what is important in the long-term care for persons with severe brain injury. For example, Lollar et al. underlined the use of outcome measures in children and young adults which reflect the dimensions of the International Classification of Functions (ICF), in terms of functions, capabilities and participation[20]. As we have demonstrated, the DRS offers more possibilities to do so than the GOSE and should preferably be used in long-term outcome studies in young patients with severe brain injury.

Limitations

The dropout rate in this long-term outcome study was considerable. However, compared to other studies, the participation in this study was relatively high[3], possibly because we asked cooperation and participation of family members as a replacement for of the

patients themselves. Furthermore, the results showed that the studied group did not differ significantly in important injury and demographic variables from the group of patients that did not participate. All in all, the effects of the dropout rate on the results seem to be negligible.
The time since injury varied widely in this study: between 2.4 and 15.7 years.
The longer ago, the greater the possibilities that all kinds of other life events have had influence on the recovery process. This might result in a lessening, but also in a worsening of the effects of brain injury per se. It is not possible to control this variability. Only in a prospective longitudinal study fixed measure points are possible, but even then, life events differ amongst participants, making it difficult to control.

Conclusions

In conclusion, this study proved that patients who suffered a severe traumatic brain injury might have reasonable chances for long-term independency, when early intensive neurorehabilitation is applied even when the patient is still in an unconscious state. It is supposed that the application of a structured early intensive neurorehabilitation programme contributed to the recovery. Patients with a non-traumatic brain injury who were in a vegetative state for more than two months did not demonstrate these possibilities for long-term recovery.
The comparison between the GOSE and the DRS of measuring the long-term level of social participation showed that the DRS has advantages above the GOSE in patients with severe brain injury. Especially the single items 7 and 8, concerning functionality (item 7) and employability/educationability (item 8) were able to differentiate between different levels.
Suggestions for future research are, above all, longitudinal prospective multi-centre outcome studies in which severe brain-injured patients are followed from admittance in the hospital up until five to ten years after the injury.

Competing interests

HE was the clinical psychologist of most of the patients during their treatment period at the rehabilitation centre, but had no contact with them in this study.
No other competing interests were present.

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CHAPTER 7

Long-term quality of life and depression after severe brain injury in young patients in relation to coping styles of close relatives

Submitted for publication
H.J. Eilander, C.M. van Heugten, P.L.M. de Kort, V. Bartray, A.J.H. Prevo

Abstract

Objective
Severe brain injury results in prolonged unconsciousness and generally eventually in long-term disabilities, in physical, cognitive, behavioural or social capacities. Most young patients come to live at their parents' homes, even in young adulthood. It can be questioned how they rate their quality of life (QOL), whether depressions occur, and how relatives rate the QOL of their disabled relative. Moreover, it can be questioned whether the way relatives cope with the stress and burden they experience is related to their judgement about the patients' QOL.

Methods
Thirty-one patients between 2 and 25 years of age at the time of injury and one of their close relatives participated. Patients had been admitted to a rehabilitation programme for young patients in a vegetative or minimally conscious state. They all had recovered to consciousness. The investigation took place between 2.8 and 15.8 years after injury (Mean = 6.8 years). The age at investigation varied between 16.3 and 31.2 years (Mean = 22.3). Used scales were the Quality Of Life in Brain Injury scale (QOLBI), the Centre for Epidemiological Studies-Depression scale (CES-D), the Disability Rating Scale (DRS) and the Utrecht Coping List (UCL).

Results
Patients were fully or partially independent (Mean DRS score = 2.7, SD = 2.2, range 0 – 6). They were quite satisfied about their QOL (Mean QOLBI score = 7.8, SD = 1.7). Sixteen percent of them could be accounted for as being in a depressive mood. Relatives were somewhat less positive about the patients' QOL (Mean QOLBI score = 7.2, SD = 1.4). Correlations between patients' scores and relatives' scores on the subscales of the QOLBI varied substantially, indicating different views between patients and relatives.
Relatives use different kinds of coping styles to handle the stress and burden they experience. A strong correlation was found between the use of passive coping styles by relatives and depression and the patients' QOL on the psychological and social subscales of the QOLBI.

Conclusion
Young patients, who suffer severe brain injury and remain in an unconscious state for months, eventually can live fully or partially independent and experience a good level of quality of life. Their relatives judge the QOL somewhat lower. The use of passive coping styles by relatives seems to be of influence on the patients' mood and their appreciation of some aspects of their QOL.

Practice Implications
In the acute phase after severe brain injury, the given information to relatives should include the possibilities for living a life that can be experienced as good in terms of quality of life. Furthermore, relatives should be stimulated to use active coping styles.

Introduction

Severe brain injury, as defined by the score equal or less than eight on the Glasgow Coma Scale (GCS) at admission to the hospital[40], can cause long-lasting loss of consciousness. About 10% to 15% of patients with severe brain injury are still unconscious at 4 weeks after injury[49]. The longer someone remains unconscious, the smaller the chances are for recovery of conscious-ness, and the greater the chances are for severe functional disabilities[1]. The longstanding residual effects of severe brain injury in children and young adults, including cognitive, behavioural, social, and personality changes, have been well documented in the last decades[8,15,25,36]. Almost all children with severe brain injury experience cognitive or behavioural difficulties and 70% of them are moderately disabled[15]. Most of these children live at home, in which family members are the primary providers of care and support. More than in most other diseases, in the case of brain injury all members of the family experience the disabilities in one way or another[50]. Dealing with a child with brain injury can be difficult and stressful[10], although differences can be seen between families and between individual family members in the way they can handle the situation[23]. In general, caregivers have reported more difficulty dealing with the cognitive, behavioural, and psychological changes compared to changes in mobility or physical functioning[26]. A number of different factors contribute to the level of experienced distress. Two clusters of determinants of stress in caregivers can be identified. Firstly, on the part of the child, behavioural changes resulting in reduced levels of adaptive functioning[47], or cognitive and learning disabilities[15] are of importance Secondly, family system functioning[10] and caregiver-perceived social support[7] are of influence on the experienced distress. The way people react to stressful events is summarized with the term 'coping behaviour' or 'coping style'[37]. Inadequate coping behaviour in parents can play an important role in maintaining behavioural problems in children with brain injury, and vice versa[23]. For instance, the use of problem-solving coping strategies by the family can result in significantly lower levels of depression in the person who sustained traumatic brain injury[20].

Treatment programmes aimed at the recovery of consciousness and functional capacities of these patients and as well as at enhancing the coping capabilities of their relatives may contribute to better outcome, although no conclusive evidence could be found yet[21], partly due to small sample size and huge methodological difficulties[48].
An important question is, whether patients who recover to consciousness many months after injury, can still live a life that is worthwhile[18]. One possible way to answer this question is to study the quality of life (QOL). In the last two decades this concept has become important in health research, resulting in the conviction that a person's subjective evaluation of his satisfaction is the best way to investigate this concept, instead of using an external or 'objective' evaluation[30]. In clinical

practice it is often assumed that family members are generally less satisfied about the QOL of the patients, compared to the patients themselves.
No publications about this phenomenon in the case of severe paediatric brain injury could be found.

A treatment programme aimed at the recovery of consciousness for children and young adults in a vegetative or minimally conscious state (the Early Intensive Rehabilitation Programme, EINP) was developed as early as 1987 in the rehabilitation centre Leijpark, in Tilburg, the Netherlands[6]. Retrospective analysis of the medical files learned that over 60% of all patients, who were unconscious for at least one month after severe brain injury, returned to consciousness.
As part of a comprehensive research programme, in this study, the long-term quality of life and presence of depressive symptoms of the patients who recovered to consciousness were explored and compared to the general population scores.
Furthermore, it was explored whether relatives differ from patients in the appreciation of the QOL of the patients.
Finally, it was explored whether coping capabilities of relatives correlate with any of the QOL or depression scores.

Methods

Subjects
Subjects in this study were patients and one of their close relatives, who participated in the Early Intensive Rehabilitation Programme between 1988 and 2000. They were part of a cohort of 145 patients, described in an earlier published outcome study[6]. Ninety patients could be included in a long-term outcome study[5]. Twenty-five patients were deceased and of the remaining 65 patients, 31 fulfilled the inclusion criteria for this study: a verbal IQ of 75 or more, age above 15 years and being able to read and understand the questionnaires. They all agreed to participate in this study.

Measurements
Quality Of Life in Brain Injury scale
The Quality Of Life in Brain Injury scale (QOLBI) was originally developed in France[41]. The scale is translated by the first author in a forward-backward procedure[24] and adapted to the Dutch culture. Preliminary investigations showed satisfying reliability and validity[11,38].
Subjects are asked to indicate their level of satisfaction about different aspects of life on thirty-five questions by means of a ten-points scale, ranging from 1 (completely unsatisfied) to 10 (completely satisfied).
The questions are clustered into six domains: Physical functioning (4 items), Cognitive functioning (7 items), Psychological functioning (5 items), Functional independency (3 items), Social functioning (9 items) and Identity (6 items).
One final question ("How satisfied are you about the quality of your life in general?") was distinctively scored (General).
The QOLBI was presented in two versions: one to be completed by patients (QOLBI-P) and one version to be completed by a close relative about the quality of life of the patient (QOLBI-R).

Centre for Epidemiological Studies-Depression Scale

The Centre for Epidemiological Studies-Depression Scale (CES-D) is a 20-item instrument that was developed by the National Institute of Mental Health to detect major or clinical depression in adolescents and adults[33]. The CES-D has high internal consistency and validity[43]. We used a validated Dutch version[3]. Each item of the CES-D determines the frequency of possible depressive symptoms. Scores range from 0 (less than once a week) to 3 (five to seven days a week) and are summed up. The range of the total score varies between 0 and 60. The higher the score the more depressive symptoms exist. In general, a cut-off score above 15 is recommended for classifying someone as being in a depressive mood.

Disability Rating Scale

The Disability Rating Scale (DRS) consists of eight items, scored on a four, five or six-point scale and is meant for rating the level of disability of the patients[34].
A high score on an item indicates a low level of functioning on that aspect. The scores on the eight DRS items can be summed up to values from 0 to 29. A score of 30 is given when a patient has deceased. The raw DRS-scores can be transformed into eight category scores without losing much information[12]:
0 = No disability, 1-3 = Mildly to partially disabled, 4-6 = Moderately disabled, 7-11= Moderately severe disabled, 12-16 = Severely disabled,17-21= Extremely severe disabled, 22-29 = Vegetative state, and 30 = Deceased.
The DRS is reliable and valid[13,34] and is able to track a patient from the lowest level of unconsciousness up to independent functioning in the community. The DRS was translated into Dutch by the first author, in a forward-backward procedure[24] and adapted to be filled out by a proxy of the patient.

The Utrecht Coping List

The Utrecht Coping List (UCL) is a Dutch originated scale, which measures different forms of coping behaviour. The UCL is based on a theory that individuals have preferences for (combinations of) ways of coping in different situations: the coping style. Good reliability and validity have been reported[37].
The UCL consists of 47 items, combined into the following 7 scales: 'Active approach', 'Palliative reaction', 'Denial', 'Seeking social support', 'Passive reaction', 'Expression of emotions', and 'Comforting thoughts'. Items can be scored at one of four categories: 1 = seldom/not, 2 = sometimes, 3 = often, 4 = very often. The scale scores are calculated by summing up the items per scale and, using norm tables, transformed into one of five class-scores: very low ($\leq 5^{th}$ percentile), low (5^{th} - 20^{th} percentile), moderate (20^{th} - 80^{th} percentile), high (80 - 95^{th} percentile), and very high ($\geq 95^{th}$ percentile).

Procedures

An investigator reading aloud the questions administered the QOLBI-P and the CES-D, whilst the patient was able to read the questions also. The investigator scored the given answer. This procedure took at most one hour. At the same time in a separate room, the close relative filled out the QOLBI-R, the DRS and the UCL.

Twenty-nine of the examinations were executed in the rehabilitation centre; two were executed at the patients' homes.

Statistical analyses
Descriptive statistics such as frequency tables were used to describe the population and the outcome scores. Associations between variables were tested by the Wilcoxon Signed Ranks test. Correlation coefficients were calculated by means of Spearman's rho correlation coefficient. Alpha was set at .05.
Data were analysed with the Statistical Package for the Social Sciences (SPSS 11.5.0 and SPSS 14.0, ©SPSS Inc.)

Results

All participating patients suffered from severe brain injury and were in VS or MCS at admission to EINP. They were admitted between 22 and 168 days after injury (M = 60.7 days, SD = 30.9). At that time, their age varied between 5 and 20 years. At the time of this study (Winter 2002/2003) the age of the patients varied between 16 and 31 years. At discharge from EINP, all patients were conscious, except for one, who later became fully conscious. See Table 1 for the demographic characteristics.
After discharge from EINP, the patients participated in regular rehabilitation services for six months or more. The long-term data for the present study were collected on average 6.8 years post injury (range: 2.8 – 15.8 years).
Neuropsychological investigation revealed that all patients suffered at least one major cognitive disorder, in memory functions, attention processes, or speed of information processing (unpublished data). The DRS-scores (M = 2.7, SD = 2.2, range 0-6) showed that all patients appeared to be partially or fully independent, according to their relatives. The highest raw score of 6 results in a category score of moderately disabled, indicating that the patients need supervision in daily activities and are restricted in the choice of jobs or only able to work in a sheltered environment.

Most of the participating relatives were female, 22 of them being the mother of the patients. In one case, a sister participated as closest relative and in another case the partner.

Long-term quality of life and depression as experienced by patients
The experienced quality of life of the patients is good: the mean score on the General question is 7.8 (SD=1.7), with 16% of the patients being unsatisfied (score 5) and 19% of them being fully satisfied (score 10) about their lives. The mean scores on the subscales vary between 6.8 for the cognitive aspect and 7.9 for the functional aspect (see Table 2). Five of the 31 patients (16.1%) scored above the cut-off point of the CES-D (i.e. 15) and could be accounted for as being in a depressive mood.

Quality of life

Table 1. Demographic characteristics patients and family members (n=31)

General	**N (%)[1]**
Time since injury	6.8 years (SD = 2.9) (range 2.8-15.8)
Patients	
Mean age at admission to EINP	15.5 years (SD = 3.9)
Mean age at examination	22.3 years (SD = 3.4)
Gender	
Male / Female	20 / 11 (64 / 36)
Cause	
Traumatic / non-traumatic	27 / 4 (87 / 13)
LOC at admission to EINP[2]	
Vegetative state	9 (29)
Minimally conscious state	22 (71)
LOC at discharge from EINP	
Vegetative state	0 (0)
Minimally conscious state	1(3)
Conscious state	30 (97)
Family members	
Gender	
Male / Female	8 / 23 (26 / 74)
Relationship to patients	
Mother	22 (71)
Father	7 (23)
Other	2 (6)
Mean age (N = 29; 2 missing)	48.0 years (SD = 8.5) (range 22 – 60)

[1] Figures are numbers and (between brackets) percentages, except when otherwise specified
[2] LOC = Level Of Consciousness

Quality of life

Table 2. Patients' quality of life (QOLBI-P) and depression (CES-D) scores

Variable	Mean (SD)	Range
QOLBI-P		
General	7.8 (1.7)	5 - 10
Physical	7.4 (1.3)	4.0 - 9.3
Cognitive	6.8 (1.1)	3.7 - 8.7
Psychological	7.7 (1.3)	4.4 - 9.6
Functional	7.9 (1.7)	3.5 - 10.0
Social	7.7 (1.3)	5.0 - 10.0
Identity	7.4 (1.4)	4.6 - 9.5
CES-D	7.8 (9.4)	0 - 36

Most of the variables of the QOLBI-P are strongly correlated to each other, showing a high internal consistency (see Table 3). Remarkable is the absence of any correlation between the QOLBI functional scale with the cognitive and psychological scales. The CES-D scores strongly correlated with five of the QOLBI-P scales: the General question, and the Cognitive, Psychological, Social and Identity scales. Remarkably, no relationship at all could be found between the CES-D and the experienced QOL on the Functional scale (rho = -.09), meaning that depressive feelings were not generated by the level of satisfaction about functional dependency.

Table 3. Spearman's rho correlations of patients' scales

	QOLBI-P general	QOLBI-P physical	QOLBI-P cognitive	QOLBI-P psych	QOLBI-P functional	QOLBI-P social	QOLBI-P identity
QOLBI-P physical	.57**						
QOLBI-P cognitive	.51**	.38*					
QOLBI-P psychological	.58**	.58**	.72**				
QOLBI-P functional	.44*	.51**	.18	.29			
QOLBI-P social	.75**	.64**	.66**	.83**	.35		
QOLBI-P identity	.88**	.56**	.58**	.70**	.36*	.80**	
CES-D	-.58**	-.43*	-.66**	-.70**	-.09	-.60**	-.67**

* $p < .05$; ** $p < .01$

Long-term quality of life of patients, as experienced by relatives

In general, relatives seem to be quite satisfied about the patients' QOL: the mean score on the General question is 7.2 (SD=1.4), with13% of the family members being unsatisfied (score 5) and 7% of them being fully satisfied (score 10) about the

lives of the patients. The views of the relatives about the cognitive aspect are relatively low, with 45% of them scoring below 6 (see Table 4).

Table 4. Relatives' scores about the quality of life of patients (QOLBI-R)

Variable	Mean (SD)	Range
QOLBI-R		
General	7.2 (1.4)	5 - 10
Physical	6.8 (1.4)	3.5 - 10.0
Cognitive	6.0 (1.3)	3.6 - 8.3
Psychological	7.2 (1.1)	4.2 - 10.0
Functional	6.8 (2.2)	2.0 - 10.0
Social	7.2 (1.2)	3.2 - 9.8
Identity	6.9 (1.4)	3.7 - 10.0

There are remarkable differences in the different correlations between the scales of the QOLBI-R (see Table 5). Only seven of the possible 21 correlations show a p-value $< .01$ and eight of the correlations are not significant at all. The QOLBI-R identity scale correlated strongly with five other scales (general, physical, cognitive and social), whilst the psychological scale only correlated weakly with two other scales (general and cognitive).
The DRS-scores as given by the relatives show strong correlations with three scales of the QOLBI-R: the General question, and the Functional and Identity scales and some weaker correlations with two other scales: Cognitive and Social. No correlations were found with the Physical and Psychological scales.

Table 5. Spearman's rho correlations of relatives' scales

	QOLBI-R general	QOLBI-R physical	QOLBI-R cognitive	QOLBI-R psych	QOLBI-R functional	QOLBI-R social	QOLBI-R identity
QOLBI-R physical	.29						
QOLBI-R cognitive	.53**	.30					
QOLBI-R psychological	.45*	-.09	.41*				
QOLBI-R functional	.38*	.30	.37*	.10			
QOLBI-R social	.53**	.43*	.48**	.25	.45*		
QOLBI-R identity	.82**	.48**	.53**	.34	.36	.75**	
DRS	-.49**	-.13	-.38*	-.14	-.48**	-.41*	-.63**

* $p < .05$; ** $p < .01$

Coping styles of relatives
Figure 1 shows the distributions of the scores on the seven coping scales of the UCL. Almost 50% of the relatives use an active approach and about 45% make use of the expression of emotions to cope with the situation. In addition, about 80% of the relatives also use 'seek distraction' and make use of general stimulants as smoking or drinking (Palliative reaction) to cope with the situation.

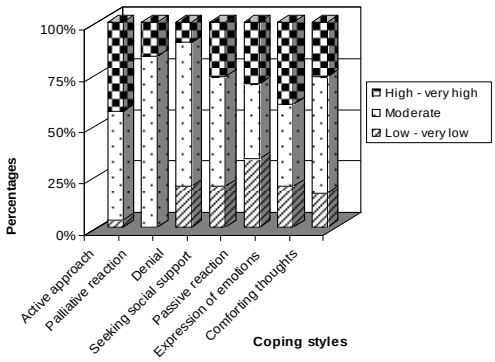

Figure 1. Frequencies of the scores of the relatives on the UCL categories

Comparison of QOLBI-scores between patients and relatives
On all scales of the QOLBI and on the General question, the scores of the relatives are lower, compared to the scores of the patients (see Tables 2 and 4). Statistical analysis showed that the differences are significant on four of the seven scales: Physical ($p = .04$), Cognitive ($p = .01$), Functional ($p = .03$), and Social ($p = .05$).

Correlations between patients' and relatives' variables
As can be seen in Table 6, the pattern of correlations between the scores of the patients on the QOLBI-P and the scores of the relatives on the QOLBI-R is irregular. Some of the parallel subscales even show no correlation at all, as is the case between the cognitive and the functional scales. Apparently, patients differ widely from relatives in the appreciation of their capabilities.

On the other hand, some apparently non-related scales, like the QOLBI-R social and the QOLBI-P physical and QOLBI-P functional show strong correlations.
Of all possible correlations between patients' and relatives' variables, only six show an alpha of 1% or less. Both QOLBI General scores showed a strong correlation (rho = .47), as well as the QOLBI-R Social scale with the QOLBI-P Physical (rho = .50) and Functional (rho = .51) scales, as can be seen in Table 6. Also, the UCL Passive reaction scale showed a strong negative correlation with three of the patients' scales: QOLBI-P Psychological (rho = -.48), QOLBI-P Social (rho = -.49) and the CES-D (rho = -.57).
None of the QOLBI-P scales, or the CES-D correlated significantly with the DRS-scores as given by the relatives, except for the QOLBI-P functional scale: the Spearman rho is -.43 ($p < .05$). Remarkably, all correlations between the DRS and the other QOLBI scales are very low (< -.15), or even zero (in case of the QOLBI-p general and psychological scales).
The correlation between the CES-D and the DRS is -.21 ($p = .26$), which confirms the finding that the level of functional independency is not related to any feelings of well-being.

Table 6. Spearman's rho correlations between QOLBI-P and QOLBI-R scales

	QOLBI-R general	QOLBI-R physical	QOLBI-R cognitive	QOLBI-R psych	QOLBI-R functional	QOLBI-R social	QOLBI-R identity
QOLBI-P general	.47**	.09	-.06	.13	.03	.39*	.34
QOLBI-P physical	.31	.39*	.00	.29	.23	.50**	.41*
QOLBI-P cognitive	.30	.08	.20	.40*	-.00	.39*	.22
QOLBI-P psychological	.34	-.00	-.16	.36*	.02	.31	.32
QOLBI-P functional	.33	.15	.10	.14	.19	.51**	.40*
QOLBI-P social	.40*	-.03	-.10	.33	.05	.44*	.38*
QOLBI-P identity	.41*	.04	-.09	.23	.00	.39*	.37*

Discussion and conclusions

In this study, the experienced quality of life by the patients appeared to be quite high, despite the fact that they suffered severe brain injury and most of them encountered long-term consequences. Although no gold standard exits[44], the scores can be accounted for as within the normal range. A possible explanation is the fact that patients who experience many limitations in daily life and need support, tend to score better on QOL-scale compared to patients who have less limitations[4]. It is possible that the studied group falls into that category, although the scores on the DRS suggest that a majority of the patients do not need much support in daily life. Another explanation can be found in a response shift. It appears that people whose health status changes, also change their internal standards and values on the construct of quality of life[35]. This may even result in reporting higher QOL by patients than do healthy individuals[42]. It can be expected that these phenomena also are apparent in this study. The process of adaptation to the new situation probably takes some years. Recently Power et al. demonstrated that 10-12 years post-injury, patients have grown in their skills to adapt to the new situation compared to 1-3 years post-injury[31]. Another possible explanation is the special population of patients that was involved in this study. They all suffered severe brain injury and remained in VS or MCS for at least one month. In the acute phase, their chances for survival were small and in the recovery phase, the outlook on an

independent life was negative. Living (almost) fully independent at the time of this study was not expected. Therefore, it can be hypothesized that the patients and their relatives enjoy life much more then other people, when they take the original expectancies into account.

In this study, the proportion of patients who showed depressive symptoms (16%) seems to be lower than in similar studies (25-38%)[15,17], but is somewhat higher compared to the community based rate (6-10%)[17,39]. As in other studies, the relationship between depressive symptoms and experienced QOL is strong [16]. Remarkably, the presence of depressive symptoms is not related to the experienced QOL on the functional scale and weakly related to the experienced QOL on the physical scale. The psycho-social experienced QOL appears to be far more important.
Overall, it can be concluded that the partition of the cohort who participated EINP, in general live a life that is worthwhile, according to their own opinion.

Further findings of this study are the differences in perceived quality of life of the patients between themselves and the relatives. Three possible explanations can be postulated. Firstly, the patients who participated suffered severe brain injury. All had intellectual or cognitive deficits (unpublished data) and it cannot be ruled out that in some of the patients these deficits interfered with the measurements. However, the assessment was done by a researcher, who carefully prepared the interview, as was suggested by Paterson & Scott-Findlay[28], and monitored the reliability of the answering as good as possible[32].
Secondly, almost half of the patients (39.7%) were moderately disabled, needing substantial help during the day It can be assumed that most of the help was invested in the most difficult parts of living, i.e. finances, planning, solving difficult situations. Therefore, the patients probably did not experience too much negative situations and were not quite aware of their deficits, resulting in a rather high level of the experienced quality of life[22]. The last possible explanation of the found differences is the experienced burden by relatives, who often are involved in caring for their relative with brain injury. Relatives have to do the difficult jobs, and in their contacts with the patient, they should always take the deficits of the patients into account. Although no relation was found between time since injury or age of the relatives with one of the QOLBI- or UCL-scales, it still can be assumed that long-time caring causes much higher levels of stress. This experienced stress can have had influence on the judgement about the patients' quality of life.
All these explanations are rather speculative. This study cannot rule out one of these possible explanations, stressing the need to do more extensive studies on this topic.

The final objective of this study concerned the coping capacities of the relatives, which appeared to vary substantially. A majority of the relatives used all coping styles at least occasionally. Most of the relatives needed to seek some distraction and made use of general stimulants as

smoking or drinking, but a great majority did this in a moderate way. Furthermore, two different coping styles seemed to be used: either an active approach or a more passive style like making use of comforting thoughts or seeking social support. In other studies, it was demonstrated that the use of active copings styles diminishes stress and ameliorate the experienced quality of life[14,26]. This phenomenon was not confirmed in this study: no correlation at all was found between the active coping style of relatives and any quality of life variable. A possible explanation is the way relatives were treated. As a fundamental ingredient of EINP, all parents, brothers, sisters, and partners had been extensively informed about the effects of severe brain injury and about the way they could avoid negative effects in the long-term. When necessary, the family system as a whole was addressed[19]. The results of this study show that all relatives at least make use of an active copings style in a moderate way, perhaps reflecting the result of the treatment procedures.
The use of passive coping styles seems to be related to a diminished quality of life[45]. This phenomenon was partly found in this study. The expression of a passive coping style correlated moderately to the judgement of the relatives about the social aspects of the patients' quality of life. Moreover, a passive coping style of relatives correlated strongly with feelings of depression by patients and with their own judgement about social and psychological aspects of the quality of life. It is not possible to determine for sure by this study what comes first, but it can be assumed that the way relatives behave is of influence on the mood and judgement of the patients[29]. Therefore, from this study the conclusion can be drawn that it is important to avoid a passive coping style in relatives to enhance the experienced long-term quality of life in patients who sustain severe brain injury.

Limitations

Firstly, the studied group was small, whereas the time since injury varied hugely. It is possible that this aspect partly causes variations in scores. Recently Powell found, that on the long-term (10-12 years post injury) compared to the short-term (1-3 years post-injury), patients show intrapersonal growth in aspects such as: relating to others, personal strength, new possibilities, appreciation of life and spirituality[31]. It can be hypothesized that this growth also occurred in some of the patients and relatives in this study. Our studied group is too small to control for this aspect. However, large-scale comprehensive studies in this area do not exist, which makes the present study valuable.

Secondly, the used scale to measure the quality of life, the QOLBI, has only marginally been studied on aspects of reliability and validity. No item analysis could be executed, nor any factor analysis. It cannot be excluded that the constructed subscales have a somewhat different meaning than assumed. Nevertheless, at the time of this study, no other scale is known that is specially designed for brain-injured patients. The WHOQOL, a worldwide used generic scale to investigate the quality of life[2,46] is too

extensive and in certain aspects not specific enough to be solely used in brain injured patients[27]. Therefore, no alternative was present but the QOLBI to be used in this study. It can be assumed, given the same trends as in other studies, that the results at least give a good indication of the development of the experienced quality of life in the studied group.

Recommendations

The most important conclusion out of this study is to avoid using passive coping styles in concurring major life problems. Therefore, we recommend clinicians to teach relatives to use problem solving strategies related to an active coping style. Secondly, the fact that on the long-term patients are able to experience high levels of quality of life should be incorporated in the information provided in the acute phase. This will provide a more positive mood in relatives, which is important for psychological well-being[13] and for avoiding the development of depression in patients.

Further research is needed on the time factor on the experienced quality of life. Especially of importance is, whether it is time alone, or whether provided help or changed situations contribute to changes over time in the experienced quality of life.

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CHAPTER 8

General discussion and conclusions

This thesis demonstrates the complexity of the topics involved in treatment and research in young patients in a vegetative state (VS) or a minimally conscious state (MCS). The type of trauma, the incidence, the various levels of consciousness, the recovery processes, the family involvement, the various outcome measures and the quality of life are all topics with difficult aspects regarding the goals of this thesis.

Ultimately, three general themes have been investigated in this thesis.
Firstly, the focus was directed to the concept of the successive levels of consciousness during recovery, including the development of an observation scale: the Post-Acute Level of Consciousness scale (PALOC-s). By using this scale, it was possible to reliably establish the recovery of consciousness of young patients in VS or MCS one month after suffering from a traumatic brain injury (TBI).
Secondly, the outcome in terms of level of consciousness of the patients who participated in EINP was studied. It was investigated whether EINP contributed to the outcome scores and whether recovery to consciousness could be predicted.
Thirdly, the long-term outcome, social participation and quality of life of the patients together with the involvement and coping strategies of family members was evaluated.

Levels of consciousness and PALOC-s

Insight is increasing concerning the gradual recovery of consciousness from coma after severe brain injury, along distinctive stages of consciousness[23,30]. In 1996, the concepts of the Vegetative State and the Minimally Conscious State are elaborated to be able to make distinctions between patients who show distinctive behaviour[1,8]. Nevertheless, discussions continue about the nature of both states and about possible sublevels within each state[10,26], partly fuelled by recent developments with fMRI-studies, showing brain activity related to commands and questions in some vegetative and minimally conscious patients[15].
A reliable and valid assessment of the distinctive stages of gradual recovery is therefore of great importance for clinical management of these patients[16]. From our study, described in *chapter 2,* we conclude that it is possible to investigate the accurate level of recovery of consciousness in young patients with a prolonged unconscious state after severe brain injury by using the Post-Acute Level Of Consciousness scale (PALOC-s). This scale offers both clinicians and researchers the opportunity to discriminate subtle differences in the behaviour of unconscious patients, especially when changes are marginal and recovery is very slow or difficult to observe. The PALOC-s has some important advantages compared with other frequently used similar scales.
In hospitals, generally the Glasgow Coma Scale (GCS[31]) is used to measure the depth of the unconscious state. However, this scale is only validated for the acute state and is not able to distinguish sublevels of consciousness.
Currently in post-acute care, the JFK Coma Recovery Scale-revised (CRS-r) is often used[9,14]. This scale also offers the

possibility to distinguish between VS and MCS and has distinctive subscales to determine differences in type of behaviour in patients. A disadvantage compared to the PALOC-s, which can be scored by the treatment team within seconds, is the length and complexity of the administration of the CRS-r, which takes about 30-60 minutes. Together, both of these scales seem to be very helpful in the management of patients in VS or MCS.

Incidence

The incidence of young TBI patients, who were still in VS or MCS at one month after injury, appeared to be surprisingly low (*chapter 3*). The calculated incidence in our study of 5-6 patients per million population (PMP), including TBI as well as non-TBI, contrasts with the calculations of Ashwal[3]. He estimated the worldwide average prevalence of children under the age of 15 in VS being about 49 PMP (range 6-80). Although Ashwal presented the figures as being for children in VS, it can be assumed that also children in MCS were included in the calculations, as most of the underlying studies were done before the introduction of the concept of MCS. Explanations for the low incidence can only be speculative. Perhaps, in earlier studies patients were included who did not fulfil the criteria for VS or MCS, but (for instance) suffered from long-lasting post-traumatic amnesia (PTA)[30], being unable to communicate or cooperate sufficiently. Another possible explanation is that in recent years the treatment protocols in the ICU's in the Netherlands have led to more reliable prediction of recovery[12], this resulting in the termination of care and treatment within the first weeks after injury in patients who would otherwise remain in VS for longer periods. Our study lacks the possibility to draw any conclusions on this explanation.

The found differences are of great importance for the planning of health services. Most of the rehabilitation in the Netherlands is regionally organized. With such a low number of patients in VS or MCS, it is impossible for hospitals, rehabilitation facilities and special nursing homes all over the Netherlands to obtain the required skills on their staff. Whenever special treatment or care is needed, this can therefore only be provided in specialized facilities, admitting a substantial number of patients. As Andrews stated recently, '*the rehabilitation of the person with profound brain damage is a complex process requiring the skills of a true interdisciplinary team*'[2].

Recovery to consciousness and outcome after EINP

Recovery to consciousness after severe brain injury and a prolonged period of unconsciousness can by no means be guaranteed.
The retrospective and prospective outcome studies (*chapter 4 and chapter 5*) showed that 60% of all patients who were admitted to EINP eventually recovered to consciousness, with substantial differences between the different conditions. A great majority of the patients in MCS at admission to EINP recovered to consciousness, with better outcomes in most of the TBI categories compared to

non-TBI categories. The general outcome percentage is better than expected based on historical data[4,21,22], considering the severity of the injuries and the duration of the unconscious state.
The question whether EINP contributed to this finding can not be answered definitely. It proved impossible to find a control group of a substantial size (*chapter 3*), despite the cooperation of almost all hospitals in the Netherlands which provide acute care for severe neurotrauma patients. Therefore, no comparison could be made in the long-term outcome between patients who had been admitted to EINP with patients who had not been. The studies executed within this research project give therefore the best possible information regarding the outcome after EINP. The results suggest a possible positive effect of EINP. A decisive conclusion cannot however be drawn, according to the Cochrane review by Lombardi[19], who focussed on sensory stimulation protocols. Nevertheless, it can be assumed that the basic principles which underlie EINP (see Appendix 1) can be seen as the best possible in order to deal with this kind of patients, as was confirmed recently by Andrews[2]. He summed up and elaborated the main basic concepts to achieve the optimal level of recovery or improvement, all very similar to the principles of EINP:

- To provide the optimal environment for recovery;
- To prevent and treat secondary complications;
- To modify the environment - including regulating the amount of stimulation;
- To include in treatment all kinds of therapies, including medical, psychological, technological therapies and physiotherapy;
- To support the family.

It is straightforward that all of these aspects act upon each other, making it very difficult to identify individual factors which are of influence on the recovery processes. It can be assumed that the combination of activities and therapies, executed by an experienced interdisciplinary team generated the possible results. However, the possible effect of just one single factor cannot be excluded. For instance, recently it has been shown that electrical thalamic stimulation can improve behaviour in a patient in MCS[27]. The sensory stimulation activities in EINP are targeted on thalamic functioning, possibly having the same effects as electrical stimulation.

One-third of the patients did not recover to consciousness and remained in VS or MCS. For them, the EINP did not offer any possibilities for recovery. It can be assumed that at least their families were very disappointed about the results. The question that remains is whether it is ethical to give families any hope for recovery, when the chances for it are rather small[6]. In a recent small qualitative study it was found that relatives of severe brain injured patients generally appreciated honest, clear and continuous information about the condition of the

patient[13]. It appeared to be important to relatives that bad news should be conveyed in a polite manner, without depriving them of hope. It can be assumed that a combination of providing a possible beneficial therapy to the patient, and informing relatives as detailed as possible, prevents the relatives to develop unnecessary extra psychological stress. This may result in the end, as Lavrijsen suggested[17], in making decisions regarding withdrawal of all medical treatment in order to prevent patients staying in a vegetative state for years.

Prediction of recovery

It is of great clinical importance to predict the outcome after EINP in an early stage. This would prevent the creation of false expectations in the minds of relatives, when there are actually no possibilities for recovery, perhaps also preventing the establishment of strong bonds with the patient in a vegetative state[18]. In cases where there is no chance for any recovery, it would be more appropriate to talk with families about the termination of treatment, although this would be difficult[5].
To predict outcome, the relevant variables have to be identified. This study has made this partly possible.
Firstly, the level of consciousness at admission appeared to be highly predictive for recovery to consciousness. In the prospective outcome study (*chapter 5*), all patients in MCS or in a VS high active state (PALOC-s: 4) recovered to consciousness. This makes it possible in a very early stage to prepare patients and their relatives for further rehabilitation.
Of the patients in a VS very little responsive or reflexive state (PALOC-s: 2 or 3), half recovered to consciousness and the other half did not. When chances for recovery in this group of patients could be established, treatments could be reliably adapted to the expected outcome.
Secondly, we found that about one-third of all patients remained in VS or MCS (*chapter 4 and chapter 5)* and did not show any progress. For them, EINP was not successful concerning recovery to consciousness. An important question is what factors play a role and whether these factors can be identified in an early stage. The study offers no possibilities to identify all probable factors that cause the lack of recovery. Some of them, however, could be identified (*chapter 4*). The most important one was 'type of trauma'. Patients who suffered a non-traumatic injury had a 6-time slighter chance to recover to consciousness. Probably the different mechanisms of injury play an important role. Brain injury can be seen as a process, rather than an event[25]. The resulting lesions in non-traumatic injury are generally more scattered throughout the whole brain and of influence on the basic metabolic homeostasis. Disrupting this homeostasis, especially causing anoxia, may result in damages all over the brain, compared to the focal contusional damage in most of the patients who suffer a traumatic injury[24].

Rate of recovery

The prospective outcome study (*chapter 5*) showed that over time of EINP, three different recovery rates could be seen. Firstly, no recovery of the level of consciousness at all was seen in 12 patients in VS. This phenomenon did not happen in patients in MCS. Secondly, there appeared to be a group of 11 patients in VS or MCS who showed quick (within a month) recovery to consciousness. And finally, 21 patients in VS or MCS made gradually progress in the level of consciousness.
Neither age, gender, the initial Glasgow Coma Scale score (GCS)[31], the cause of the injury, nor the length of stay at the ICU, predicted the rate of recovery. The only observable difference was the mean level of consciousness at admission of each of the identifiable groups. However, the amount of variation within each group prevents making a reliable prediction about the rate of recovery for each patient individually.

All in all, two factors are important in prediction of possible recovery: the level of consciousness at admission and the type of trauma. Nevertheless, false positive or false negative predictions are still possible in patients who are in VS very little responsive or reflexive state (PALOC-s: 2 or 3)
One possible method to improve the prediction furthermore, is to make use of neurophysiologic parameters. In the overall research design, this kind of investigation was included[7]. Separate from this thesis, Wijnen recently published about that part of the project[35]. The most promising finding was the correlation between the so-called Mismatch Negativity (MMN) at admission to EINP and the level of consciousness at discharge. The MMN is an EEG-based measurement, which signifies the potential of the brain to notice differences between two stimuli. This capacity is supposed to function beyond the level of consciousness. In 10 patients who were subjected to an auditory based protocol, there appeared to be a one-to-one relation between the presence of the MMN at admission to EINP and becoming conscious[36], regardless of the level of consciousness at admission.

Long-term outcome and quality of life

The long-term outcome study (*chapter 6*) showed that the Disability Rating Scale (DRS) offers the best possibilities to investigate the functional state of the patients.
It appeared that in the long run, about 20% of the TBI patients and 50% of the non-TBI patients had died. Patients in VS at discharge from EINP died within a couple of years, as did one quarter of the patients in MCS, resulting in only a small number of patients remaining in MCS for several years. The study cannot answer questions concerning what causes the death of the patients. The most probable explanations are in most cases the proceeding of complications[11] or the

termination of treatment in specific patients[18]. A great majority of the surviving patients regained some level of independency, some of them living on their own and participating fully in society. Nevertheless, all patients suffered in the long-term from one or more cognitive problems. Of the non-TBI patients, half remained completely dependent. Of the patients who were able to fill in relevant questionnaires, most of them expressed a relative high level of experienced quality of life *(chapter 7)*. Although no gold standard exits[33], the scores can be accounted for as within the normal range. This is contrary to some earlier expressed ideas about the emotional state patients would come in after emerging from a vegetative state[6,20]. The question whether EINP contributed to this phenomenon cannot be answered. It is a fact that in EINP much attention has been given to the emotional state of patients who recover to consciousness and to the emotional state of the relatives, striving for a positive mood about themselves. Therapists in EINP intended to establish positive bonds with patients and their relatives, what can contribute to the outcome in terms of level of functioning and of satisfaction about what has been established[28].

The general conclusion can be made that none of the patients who participated in EINP remained in VS for many years and that patients who became conscious in general are content with their lives.

Family

Although the scores of family members about the patients' quality of life are somewhat lower than the scores of the patients themselves, in general relatives are content with the patients' situation *(chapter 7)*. Recently it was revealed that the judgement of relatives concerning possible negative changes in the patients behaviours and personalities is highly related to the feelings of anger about what has happened and about situations in daily life that are stressful to them[34]. This 'anger-factor' contributed ten times stronger than injury severity to the judgement of relatives.
Expressing emotions is one way to cope with stressful situations[29]. Other coping styles are either more passive or more active. The use of active coping styles generally is supposed to be highly correlated to a more positive attitude to stressful situations[32]. In this study it was shown that about 50% of the relatives made use of active coping strategies and 80% of them made use of distraction or general stimulants like smoking and drinking to cope with the situation. We did not find any correlations between coping styles and judgement of the patients' well-being.
It can be concluded that the relation between coping and perceived quality of life is complicated and should be studied more thoroughly than was possible in this study.

Methodological considerations

This research project faced methodological problems.
The project is developed and executed within the clinical setting of a small rehabilitation centre, lacking the facilities to control all different variables.
Not being able to create a control group condition, neither retrospectively nor prospectively, was a major disadvantage for drawing firm conclusions.
Inevitably, the research resulted in an observational study in which different aspects have been studied, without the possibilities to compare the data between different controlled conditions. The outcome studies included heterogeneous cohorts (age, cause of injury, time since injury, co-morbidity) resulting in small subgroups.
As a consequence of these methodological limitations, various methods had to be used being able to evaluate EINP.
The combination of a retrospective and a prospective outcome study makes it somewhat questionable whether the results can be compared, especially since the development of the PALOC-s only took place during the prospective study. Furthermore, the evaluation period extended over 14 years. The treatments and the processes within the acute care have probably been changed over time. The same accounts for the details within EINP. It is assumable that all these changes affected the long-term outcome.

Finally, parts of the outcome data were based on medical files instead of real-time measurements. It is questionable whether all data in the files were fully reliable, as they were provided by different people. It was not possible to check the reliability of the data.

Despite the drawbacks, the study contributes highly to the clinical and scientific knowledge about young persons in VS or MCS. As far as we know, this is the first large scale study ever conducted in which this type of patient is studied in such quantities and with such different measurements, especially when the neurophysiological studies are incorporated. The fact that of 90 patients the long-term outcome so many years after injury could be identified is also of great importance.

The prospective study, using the repeated measurements as evaluation method, gives good insight in recovery processes in the sub-acute state. The identification of three different recovery patterns can be useful to clinicians who are asking what to expect in different type of patients.

The development of the PALOC-s is of great value for the evaluation of patients and bears the possibility to become one of the standards to be used in clinical practice as well as in research.

Finally, the study in which the incidence of young patients in VS or MCS could be established is of great importance. The

cooperation of 23 of the 24 possible hospitals made this study strong and worthwhile. The found figures are highly reliable and form a good base for planning of future facilities.

Recommendations

Clinical

Although definitive proof of its efficacy is lacking, the results of this study are sufficient to recommend the application of EINP for all patients in VS or MCS, as soon as possible after emerging from the comatose state. Although in this study only young persons up to 25 years of age were included, it may be that the recovery processes are also present in adult patients. It appears not be justified to withhold this kind of treatment to adult patients. EINP should be provided in special clinics, by an experienced interdisciplinary team.

Research

Further research is recommended on the following aspects:

- The usefulness of the PALOC-s, as soon as patients are no longer in the acute phase after the injury
- The predictive value of the PALOC-s in combination with the use of the Mismatch Negativity
- Executing a multi-centre case-controlled control group study for evaluating EINP
- The influence of close relatives on the recovery processes
- The efficacy of EINP in adult patients.

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Epilogue

Epilogue

This research project was originated during the development of EINP in 1987. From the start, it was recognized that evaluation of the recovery processes was important. It appeared to be very difficult to develop a valid and reliable research design within the clinical context of a small (paediatric) rehabilitation centre.

Now, 20 years and a lot of hard work later, it can be concluded that all the efforts of so many at last were successful. Based on this research project, recently the Health Insurance companies have labelled EINP as covered treatment for young patients in a vegetative or minimally conscious state. Twenty years ago, nobody could have thought that this would be the result of the development of one single treatment programme for one single five-year old girl.

I therefore end this thesis with the statement that *"miracles don't exist, unless you are doing the hard job"*.

Summary

Summary

The research, described in this thesis was focused on the evaluation of the "Early Intensive Neurorehabilitation" (EINP) treatment programme, which was developed in 1987. This clinical treatment programme for children and adolescents in a vegetative state or minimally conscious state after severe brain injury takes place in the paediatric rehabilitation department of the Rehabilitation Centre Leijpark (RCL). An observational scale was developed to measure and evaluate the level of consciousness and the amount of recovery of consciousness. Long term functional recovery and patient experienced quality of life was investigated. The patient quality of life was also judged by family members. Family members coping style and the influence on the wellbeing of the patients was investigated.

In the Preface, the story of Annelot and her father Frank is told. They explain what happened to Annelot, how her parents reacted to the situation and the recovery process she went through. The EINP programme is in short described.

In Chapter 1 the theoretical background of the research is described and the subject matter of chapters 2 through 8 are introduced: the epidemiology of severe brain injury, the terms 'vegetative state (VS)' and 'minimally conscious state (MCS)' and their mutual connection, the possibility of categorizing the states of consciousness, the recovery processes, the long term consequences of severe brain injury, the experienced quality of life, the consequences for family members and the treatment opportunities for persons in VS or MCS. Lastly the methodological problems of conducting the evaluation study are indicated briefly.

In Chapter 2 the development and validation of the Post-Acute Level Of Consciousness scale (PALOC-s) is described. This scale is based on international publications which half way through the 1990's shed more insight on the issues concerning persons with loss of consciousness after severe brain injury. In the PALOC-s, eight levels of consciousness ranging from coma to full consciousness are distinguished. The validation was done using video recordings of repeated assessments on the levels of conscious of 44 patients ranging in age from 2 to 25 years. The assessments were conducted every two weeks using the Western Neuro Sensory Stimulation Profile (WNSSP). The Disability Rating Scale (DRS) was also conducted. In total, 327 recorded assessments were available for use. Six independent raters worked on three phases to establish the inter-rater reliability, the test-retest reliability and the validity of the PALOC-s. Furthermore, by using the PALOC-s scores that were obtained during the patients' assessment, the responsivity was determined.
The reliability of the PALOC-s ended up being high. The inter-rater reliability scores varied between 0.82 and 0.95. The validation was also high: the correlations between the PALOC-s scores of the six raters with the WNSSP-scores varied

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between 0.88 and 0.93, and with the DRS-scores between 0.75 and 0.88. Finally, the responsivity was high (t=8.2) with a standardised effect size of 1.30. The conclusion in this chapter is that the PALOC-s is a trustworthy, valid and responsive instrument and can be used to systematically assess the level of consciousness of long-term unconscious patients. The PALOC-s can be used in clinical practice as well as in scientific research.

Chapter 3 describes the approach to find a case-controlled control group containing patients who were not admitted to the EINP programme. An investigation was conducted using the medical dossiers of patients younger than 25 who suffered severe brain injury following an accident between December 2000 and June 2003, who were still in a vegetative or minimally conscious state one month after the accident and who were admitted to one of the 24 hospitals in The Netherlands with a neurological intensive care unit. Twenty-three hospitals cooperated. It was the intention to determine through these patients the long-term situation in terms of consciousness and functional self-efficiency whereby a comparison could be made between the patients included in the EINP programme and the patients not included. In total there were 42 patients found. Thirty of them had been admitted to the EINP programme. A control group could not be formed due to the shortage of patients and therefore the research was stopped.

The investigation clearly indicated that the incidence of young people with a lengthy loss of consciousness following severe traumatic brain injury (3.4 per million people per year) is a lot fewer then previously presumed. This information is important for the organisation of rehabilitation and long-term services.

In Chapter 4 the characteristics of all patients who were admitted to the EINP programme between December 1987 and January 2001 was investigated, using the medical dossiers. Furthermore, the possible relationship between the most important characteristics and the level of recovery of consciousness was investigated. Two-thirds of all the admitted patients appeared to have regained consciousness, where after they were eligible for further rehabilitation. This percentage is higher than expected based on past literature findings. Patients in a vegetative state had a smaller chance of recovery than patients in a minimally conscious state. The shorter the time between injury and admittance to the EINP programme the greater the recovery chance. Finally, it appeared that patients who suffered a traumatic brain injury (TBI) also had greater chances of recovery compared to patients with brain injury caused otherwise (nTBI).

In Chapter 5, in a prospective cohort of 44 patients admitted to EINP between January 2001 and September 2003, the recovery patterns were investigated. From the time of admittance until discharge all patients

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were assessed every two weeks using the WNSSP. The level of consciousness was determined by means of the PALOC-s, and the functional situation by means of the DRS. Moreover, between 2.0 to 4.4 years after the injury both scales were also administered to investigate the long-term situation of the 32 TBI patients.
Three-quarters of all patients were in a vegetative state at admittance to EINP, two times more than in the retrospective cohort.
Three different recovery patterns were determined. One-quarter of the patients (N=12) showed no improvement whatsoever and were discharged to a nursing home or their own home in a vegetative state. Another quarter of the patients (N=11) showed quick recovery of consciousness and could be transferred to their own regional rehabilitation centre within 10 weeks after admittance to EINP. Half of the patients (N=21) displayed a variable and slower recovery process. Eventually most of these patients reached full consciousness, among which two thirds of all TBI patients. This outcome is almost two times more than was expected.
In the long run, it appeared that five of the twelve patients who were in a vegetative state at discharge had died. The seven others were no longer in a vegetative state, however they were (very) seriously disabled and fully dependent (DRS-scores 12-21). Of the TBI patients who recovered to consciousness, thirteen patients were partially disabled which means that they are slightly dependent (DRS-scores 4-11), and four patients appeared to be lightly disabled which means that they need very little help (DRS-scores 1-3).

Chapter 6 describes the long-term state of the retrospective cohort. In addition, the instrument that is best suitable to classify these long-term effects was investigated: the DRS or the Glasgow Outcome Scale Extended (GOSE). Ninety of the 145 patients or their family members participated in this study. There were no differences in the important characteristics between the group who participated and the group who did not participate. The research took place between 2.4 and 15.7 years after injury. Twenty-five patients had died by then, including almost all of the patients who were in a vegetative state at discharge. The TBI patients functioned for the most part totally or partially at a self-sufficient level. This result is better than what was expected based on historical data. The nTBI patients functioned mostly at a partially or totally dependent level. The range on the DRS is larger than on the GOSE while most of the scores in the GOSE were in the category ‘severely disabled’. It can be concluded that the DRS gives more insight in the long-term effects than the GOSE.

Chapter 7 focuses on the manifestation of depression by patients and the long-term quality of life experienced by patients, and family members points of view on these issues. Furthermore, it was investigated how family members dealt with problems and which coping styles they used. Possible correlations between these coping

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styles and the wellbeing of the patients were explored.
Thirty-one patients participated in the study which took place between 2.8 and 15.8 years after injury. The patients were 15 years and older when this study started, they had regained consciousness during the EINP programme and they all had an acceptable level of intelligence for understanding the questions. Twenty-two mothers, 7 fathers, a partner and a sister participated.
It appears that the patients on average were satisfied concerning their own quality of life: they had an average score of 7.8 on a 10-point scale. The family members score on average the patients' quality of life with a 7.2. Sixteen percent of the patients could be categorized in a depressive state. This is lower than indicated in earlier literature describing similar groups.
The presence of depression in patients is closely related to the use of passive coping styles by family members. It is assumed that this style has a negative influence on the wellbeing of the patients.
It can be concluded that patients in a vegetative state or in a minimally conscious state for a lengthy period of time can experience a good quality of life in the long-term. It is important to help family members with active problem solving strategies to cope with the problems that arise.

In Chapter 8 the most important conclusions are once again presented. It is concluded that the development of the PALOC-s and insight into the different levels of consciousness in the post-acute phase after severe brain injury are of importance for clinical practice. Furthermore, it is concluded that even though it was found that a control group could not be formed, the results from previous research showed that the EINP programme most likely provides patients with a good chance in regaining consciousness and to experience an acceptable level of long-term life quality. The incidence of children and adolescence in a vegetative state or minimally conscious state after severe brain injury seems to be very low. Therefore treatment programmes such as the EINP, demanding high quality of knowledge and experience of various team members, cannot be executed everywhere. Only specialized institutions with enough capacity are thought to be capable of providing the EINP programme at a high quality level. This study did not have enough opportunities to investigate in detail the roles and influences of family members. What is understood is that the approach the family uses concerning problems has an influence on the patients' wellbeing. The methodological shortcomings in this research are discussed and the opportunity for further research is briefly touched on. The found results are valuable and of importance for the clinical setting, especially since the EINP programme has been labelled as covered treatment through the Health Insurance companies.

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Het onderzoek in dit proefschrift was gericht op de evaluatie van het behandelprogramma 'Vroege Intensieve Neurorevalidatie (VIN)', dat sinds 1987 als klinisch behandelprogramma voor kinderen en jongeren met ernstig hersenletsel in een vegetatieve of laagbewuste toestand werd uitgevoerd, eerst in het kinderrevalidatiecentrum Charlotte Oord en vanaf 1998 binnen de sector kinderrevalidatie van Revalidatie Centrum Leijpark (RCL). Daartoe werd een observatieschaal ontwikkeld om het niveau van de bewustzijnstoestand vast te leggen en te volgen. Er werd nagegaan in welke mate herstel van het bewustzijn is opgetreden. Het functioneel herstel en de zelf ervaren kwaliteit van leven van de patiënten op de lange termijn werd onderzocht. De kwaliteit van leven van de patiënten werd tevens beoordeeld door de familieleden. De copingstijl van familieleden werd nagegaan en de invloed daarvan op het welbevinden van de patiënten.

In het Voorwoord komen Annelot en haar vader Frank aan het woord. Zij beschrijven wat er met Annelot is gebeurd, hoe ouders daarop reageerden en welk herstelproces Annelot heeft doorgemaakt. Het behandelprogramma VIN wordt kort toegelicht.

In Hoofdstuk 1 wordt de theoretische achtergrond van dit onderzoek beschreven en worden de thema's van de hoofdstukken 2 tot en met 8 geïntroduceerd: de epidemiologie van ernstig hersenletsel, de begrippen 'vegetatieve toestand (VS)' en 'laagbewuste toestand (MCS)' en de onderlinge samenhang, de mogelijkheden om die bewustzijnstoestand in kaart te brengen, de herstelprocessen, de langetermijn gevolgen van ernstig hersenletsel, de ervaren kwaliteit van leven, de gevolgen voor naaste familieleden en de behandelmogelijkheden voor mensen in VS of MCS. Ten slotte worden de methodologische problemen bij het uitvoeren van evaluatieonderzoek aangestipt.

In Hoofdstuk 2 wordt de ontwikkeling en validatie van de Post-Acute Level Of Consciousness scale (PALOC-s) beschreven. Deze schaal is gebaseerd op internationale publicaties, die halverwege de jaren negentig van de vorige eeuw meer inzicht boden in de problematiek van mensen met bewustzijnsverlies na ernstig hersenletsel. In de PALOC-s worden 8 niveaus van bewustzijn onderscheiden, van coma tot aan volledig bewustzijn.
Validatie is uitgevoerd met behulp van video-opnames van herhaalde onderzoeken van het bewustzijnsniveau van in totaal 44 patiënten tussen 2 en 25 jaar oud. De onderzoeken werden iedere twee weken uitgevoerd aan de hand van de Western Neuro Sensory Stimulation Profile (WNSSP). Tevens werd de Disability Rating Scale (DRS) afgenomen. In totaal waren 327 opgenomen onderzoeken beschikbaar. Zes onafhankelijke beoordelaars hebben in

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drie fases meegewerkt om de inter-beoordelaar betrouwbaarheid, de test-hertest betrouwbaarheid en de validiteit van de PALOC-s vast te stellen. Daarna werd met gebruikmaking van de PALOC-s scores die tijdens de onderzoeken waren bepaald, de responsiviteit vastgesteld.
De betrouwbaarheid van de PALOC-s bleek hoog. De inter-beoordelaar betrouwbaarheidscores varieerden tussen 0.82 en 0.95. De test-hertest scores varieerden tussen 0.94 en 0.96. Ook de validiteit was hoog: de correlaties tussen de PALOC-s scores van de beoordelaars met de WNSSP varieerden tussen 0.88 en 0.93, en met de DRS tussen 0.75 en 0.88. Ten slotte bleek ook de responsiviteit hoog te zijn (t=8.2) met een gestandaardiseerde effectgrootte van 1.30.
De conclusie in dit hoofdstuk is dat de PALOC-s een betrouwbaar, valide en responsief instrument is om na systematisch onderzoek het bewustzijnsniveau van langdurig bewusteloze patiënten vast te stellen. De PALOC-s is zowel in de klinische praktijk als in wetenschappelijk onderzoek bruikbaar.

In Hoofdstuk 3 wordt beschreven op welke wijze getracht is een case-controlled controle groep te vinden van patiënten die niet in het VIN-programma opgenomen zijn geweest. In 23 van alle 24 ziekenhuizen in Nederland met een neurologische intensive care afdeling is aan de hand van dossieronderzoek nagegaan welke patiënten jonger dan 25 jaar, die tussen december 2000 en juni 2003 met ernstig hersenletsel ten gevolge van een ongeval waren opgenomen, na een maand nog in een vegetatieve of laagbewuste toestand verkeerden. Het was de bedoeling om van deze mensen de langetermijn toestand in termen van bewustzijn en functionele zelfstandigheid vast te stellen, waarbij een vergelijking zou kunnen worden gemaakt tussen patiënten die wél en patiënten die niet in het VIN-programma opgenomen waren geweest.
In totaal werden 42 patiënten gevonden. Dertig van hen waren in het VIN-programma opgenomen geweest. Een controlegroep kon, door het geringe aantal, niet worden gevormd, zodat het onderzoek werd afgebroken.
Wel werd uit dit onderzoek duidelijk dat de incidentie van jonge mensen met langdurig bewustzijnsverlies na ernstig traumatisch hersenletsel (3.4 per miljoen mensen per jaar) veel lager is dan altijd werd aangenomen. Dit is van belang voor de planning van voorzieningen.

In Hoofdstuk 4 werd aan de hand van dossieronderzoek nagegaan wat de karakteristieken waren van alle patiënten die tussen december 1987 en januari 2001 in het VIN-programma opgenomen zijn geweest. Tevens werd nagegaan of er een verband bestond tussen de belangrijkste karakteristieken en de mate van herstel van het bewustzijn. Tweederde van alle opgenomen patiënten bleken weer bij bewustzijn te zijn gekomen, waarna ze in aanmerking kwamen voor verdere revalidatie. Dit percentage was hoger dan verwacht op basis van

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historische gegevens uit de literatuur. Patiënten in een vegetatieve toestand hadden een kleinere kans op herstel dan patiënten in een laagbewuste toestand. Hoe korter de tijd tussen het oplopen van het letsel en de opname in het VIN-programma, hoe groter de kans op herstel. Tenslotte bleek ook dat patiënten die een traumatisch letsel hadden opgelopen een grotere kans hadden op herstel dan patiënten met letsel op basis van een andere oorzaak.

In Hoofdstuk 5 werd het herstelpatroon onderzocht van een prospectief cohort van 44 patiënten die tussen januari 2001 en september 2003 in het VIN-programma werden opgenomen. Zij werden vanaf de aanmelding tot aan het ontslag iedere twee weken onderzocht aan de hand van de WNSSP. Het bewustzijnsniveau werd vastgesteld met behulp van de PALOC-s en de functionele toestand met behulp van de DRS. Van de 32 patiënten die traumatisch letsel hadden opgelopen, werd 2.0 tot 4.4 jaar na het trauma met behulp van beide schalen de langetermijn toestand onderzocht. Driekwart van de patiënten verkeerde bij opname in een vegetatieve toestand, twee keer zoveel als in de retrospectieve onderzoeksgroep.
Er konden drie verschillende herstelpatronen worden onderscheiden. Een kwart van de patiënten liet geen enkel herstel zien en werd in een vegetatieve toestand ontslagen naar een verpleeghuis of naar huis. Ook een kwart van de patiënten liet heel snel herstel van het bewustzijn zien en kon binnen 10 weken na opname in het VIN-programma worden ontslagen naar een revalidatieinstelling in hun eigen woonomgeving. De helft van de patiënten liet een wisselend maar trager herstelverloop zien. Uiteindelijk werden de meeste van hen volledig bewust. Tweederde van alle patiënten met traumatisch letsel herstelde tot volledig bewustzijn, bijna twee keer zoveel als verwacht.
Op de lange termijn bleken vijf van de twaalf patiënten die in vegetatieve toestand waren bij ontslag, te zijn overleden. De overige zeven verkeerden niet langer in een vegetatieve toestand, maar waren wel (zeer) ernstig gehandicapt en volledig afhankelijk (DRS-scores 12 – 21). Dertien patiënten waren matig gehandicapt, wat betekent dat ze gedeeltelijk afhankelijk zijn (DRS-scores 4 – 11). Vier patiënten bleken licht gehandicapt, wat betekent dat ze slechts op een enkel gebied hulp nodig hebben (DRS-scores 1 – 3).

In Hoofdstuk 6 wordt beschreven wat de langetermijn toestand is van het retrospectieve cohort. Ook wordt beschreven welk instrument het beste in staat is de lange termijn gevolgen in kaart te brengen: de DRS of de Glasgow Outcome Scale Extended (GOSE). Negentig van de 145 patiënten of hun familieleden werkten mee aan dit onderzoek. Er was geen verschil in belangrijke kenmerken tussen de groep die wel en de groep die niet meewerkte. Het onderzoek vond plaats tussen 2.4 en 15.7 jaar na het letsel. Vijfentwintig patiënten

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waren inmiddels overleden, waaronder vrijwel alle patiënten die in vegetatieve toestand waren gebleven. Van de patiënten met een traumatisch letsel functioneert het grootste deel op een geheel of gedeeltelijk zelfstandig niveau. Dat percentage is groter dan verwacht vergeleken met historische data. Van de patiënten met een niet-traumatisch letsel functioneert het grootste deel op een gedeeltelijk of geheel afhankelijk niveau. De spreiding op de DRS is groter dan op de GOSE, terwijl de meeste scores op de GOSE in de categorie 'ernstig gehandicapt' vielen. Geconcludeerd kan worden dat de DRS meer inzicht geeft in de langetermijn gevolgen dan de GOSE.

In Hoofdstuk 7 wordt het onderzoek besproken naar het voorkomen van depressieve klachten bij patiënten en naar de kwaliteit van leven op de lange termijn zoals die door de patiënten wordt ervaren en zoals een naast familielid daar tegen aan kijkt. Daarnaast is in dat onderzoek nagegaan hoe de familieleden omgaan met problemen, oftewel welke copingstijlen hanteren zij en of er een relatie bestaat met het welbevinden.
Aan dit onderzoek hebben 31 patiënten deelgenomen. Zij waren 15 jaar of ouder ten tijde van dit onderzoek, waren bij bewustzijn gekomen tijdens het VIN-programma en hadden een voldoende intelligentie om de vragen te begrijpen. Er deden 22 moeders, 7 vaders, een partner en een zus mee. Het onderzoek vond plaats tussen 2.8 en 15.8 jaar na het ontstaan van het letsel.
Het bleek dat de patiënten gemiddeld genomen goed tevreden waren over de eigen kwaliteit van leven: zij behaalden een gemiddelde score van 7.8 op een schaal van 10. De familieleden scoorden de kwaliteit van leven van de patiënten gemiddeld op 7.2. Zestien procent van de patiënten kan worden beschouwd als in een depressieve toestand. Dat is wat lager dan eerder in de literatuur bij vergelijkbare groepen is gevonden. De aanwezigheid van depressie bij de patiënten hangt nauw samen met het hanteren van passieve copingstijlen door familieleden. Verondersteld wordt dat dit een negatieve invloed heeft op het welbevinden van de patiënten.
Geconcludeerd wordt dat patiënten die langdurig in een vegetatieve of laagbewuste toestand verkeren op termijn een goede kwaliteit van leven kunnen ervaren. Het is van belang familieleden te helpen actieve, probleemgerichte strategieën te hanteren in het omgaan met problemen.

In Hoofdstuk 8 worden de belangrijkste conclusies uit het onderzoek weergegeven. Er wordt geconcludeerd dat de ontwikkeling van de PALOC-s en het inzicht in de verschillende niveaus van bewustzijn in de post-acute fase na ernstig hersenletsel van belang zijn voor de klinische praktijk. Verder wordt geconcludeerd dat, ondanks de bevinding dat het niet mogelijk bleek een controlegroep samen te stellen, de resultaten van het voorliggende onderzoek laat zien dat het VIN-programma aan

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patiënten zeer waarschijnlijk een goede kans biedt om tot bewustzijn te komen en op de lange termijn een voldoende niveau van kwaliteit van leven te ervaren. Omdat de gevonden incidentie van kinderen en jongeren in een vegetatieve of laagbewuste toestand na ernstig hersenletsel heel laag bleek, kan een behandeling als het VIN-programma, waarvoor veel expertise noodzakelijk is, niet overal worden toegepast. Alleen gespecialiseerde instellingen met een voldoende capaciteit worden in staat geacht het VIN-programma kwalitatief volwaardig uit te voeren.

Deze studie bood onvoldoende mogelijkheden om de rol en invloed van naaste familieleden in detail te onderzoeken. Wel is duidelijk dat de manier waarop zij met problemen omgaan van invloed is op het functioneren van patiënten.

De methodologische tekortkomingen van het onderzoek worden besproken en de mogelijkheden voor vervolgonderzoek worden aangestipt.

De gevonden resultaten zijn waardevol en van belang voor de klinische situatie, temeer daar het VIN-programma inmiddels is bestempeld als een te verzekeren prestatie krachtens de Zorgverzekeringswet.

Appendices

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Appendix 1. Short description of the Early Intensive Neurorehabilitation Programme (EINP)

The Early Intensive Neurorehabilitation Programme (EINP) is developed for the treatment of children and young adults up to 25 years of age, in a vegetative or minimally conscious state, starting as soon as possible after leaving the intensive care unit, but in any case within six months after the injury (since September 1995 within three months in case of a non-traumatic cause). The programme has to be carried out for three months, or for a shorter time when recovery of consciousness has occurred. In case of signs of recovery of consciousness, the total programme gradually changes into a cognitive learning programme, taking into account the individual needs and possibilities of the patient. The basic philosophy of the programme is that an active approach may induce recovery of brain functions in many severe injured patients, but only when all important health threats are identified and treated, and when known principles of development and growth of brain tissue are taken into account.
The treatment programme focuses on several domains:

- Improving the metabolic state, the state of nourishment, respiration, and skin condition, as well as diminishing the risk of infections[39]. The actual treatment activities depend on the individual situation of each patient. Special attention has to be given to removing invasive devices, like a tracheostomy tube or a bladder catheter.
- Recovery of the normal circadian cycles by offering a homelike environment, that is structured and filled with daily activities.
- Improving arousal and awareness by structured stimulation of all sensory modalities (vision, hearing, smell, taste, touch, posture and motion, pain, and temperature) in such a way that maximal arousal will be generated. As soon as the patient shows any voluntary reactions, reflecting a change from VS into MCS, the programme focuses on stimulation and training of cognitive functions, the contents depending on age and cognitive status.
- Improvement of normal posture and motor activities by intensive physiotherapy, occupational therapy, and oro-facial therapy, using sitting aids, a variety of splints, and other appliances.
- Improvement of the capabilities of the family to cope the situation and their own feelings, by giving support, (psycho)education, training in handling the patient, and when needed, treatment.

Each day, five treatment activities (sensory stimulation, physiotherapy, occupational therapy, oral therapy, or activity therapy) are scheduled in such a way that these activities alternate with rest, with moments of personal care, and with family visits.

Since September 1994 the programme is executed by a specialised team, consisting of a rehabilitation physician, a neuropsychologist, a stimulation therapist, physiotherapists, occupational therapists, speech therapists, nursing staff, a social worker and activity therapists. The team works according to a written protocol, describing all the steps in the programme from admission to discharge, and describing the outline of the content of the programme at the different stages of recovery.
Patients' condition and progress are evaluated in a weekly schedule, together with the whole team, resulting in changes in the kind and intensity of parts of the programme. When needed, changes have to be made on a daily basis.

Appendix 2 Post-Acute Level Of Consciousness scale (PALOC-s)

The classification presented below offers the possibility to discriminate between 8 levels of (un)conciousness in patients with severe disturbed consciousness, caused by acquired brain injury.
The PALOC-s is effective in evaluating possible changes in the level of consciousness in the post-acute phase (after the ICU-period), usually in days to weeks after the injury.

Administration of the PALOC-s is only possible in combination with a structured examination of the patient, for instance with the Western Neuro Sensory Stimulation Profile (WNSSP)[1].
The examiner should be trained and have ample knowledge and experience with severe brain-injured patients.
Scoring is completed by encircling the number that goes together with the level of consciousness, giving the most accurate reading corresponding to the patient's behaviour, as described below.

a. What is the general **level of consciousness** the patient showed during the examination?

1 2 3 4 5 6 7 8

Were there any moments during the investigation when the patient showed another level of consciousness?

b. ***Best level****:*

1 2 3 4 5 6 7 8

c. ***Worst level****:*

1 2 3 4 5 6 7 8

[1]. Ansell, B.J, J.E Keenan, and O. de la Rocha, *Western Neuro Sensory Stimulation Profile; a tool for assessing slow-to-recover head-injured patients*. 1989, Western Neuro Care Centre: Tustin, California. p. 24.

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Global Level	*Score*	PALOC-s: Description of the levels
Coma	Eyes are closed all the time. No sleep-wake cycles present.	
	1	All major body functions such as breathing, temperature regulation or blood pressure can be disturbed. Generally, no reactions are noticed after stimulation. Sometimes reflexes (stretching or flexing) are observed as a reaction to strong pain stimuli. No other reactions are present.
Vegetative State (VS)	The patient shows sleep-wake cycles, but not a proper day-night rhythm. Most of the body functions are normal. No further ventilation is required for respiration.	
	2	**Very little response (hyporesponsive)** Generally no response after stimulation. Sometimes delayed presentations of reflexes are observed.
	3	**Reflexive state** The stimuli often result in massive stretching or startle reactions, without proper habituation. Sometimes these reactions evolve into massive flexing responses. Roving eye movements can be observed, without tracking. Sometimes grimacing occurs after stimulation.
	4	*High active level and/or reactions in stimulated body parts* Generally spontaneous undirected movements. Retraction of a limb following stimulation. Orientation towards a stimulus, without fixating. Following moving persons or objects, without fixating.
Minimally Conscious State (MCS)	Patient remains awake most of the day.	
	5	*Transitional state* Following and fixating of persons and objects. Generally more directed reactions to stimuli. Behaviour is automatic, i.e. opening of the mouth when food is presented, or reaching towards persons or objects. Sometimes emotional reactions are seen such as crying or smiling towards family or to specific (known) stimuli.
	6	*Inconsistent reactions* Occasionally obeying simple commands. Total dependency. The patient has profound cognitive limitations; neuropsychological testing is impossible. Level of alertness fluctuates, but is generally low.
	7	*Consistent reactions* The patient obeys simple commands. Alertness level is high and stable. Many cognitive disturbances remain. Total dependency.
Conscious	**8**	The patient is alert and reacts spontaneously to his/her surroundings. Functional understandable mutual communication is possible, sometimes with technical support. Cognitive and behavioural disturbances can still be present.

Dankwoord

Dankwoord

Ook als het niet gebruikelijk zou zijn, zou ik er altijd voor gekozen hebben om dit dankwoord te beginnen met me te richten tot de mensen die het onderwerp zijn van dit onderzoek. De bijna 200 patiënten en honderden familieleden hebben er nooit vrijwillig voor gekozen om terecht te komen in mijn onderzoeksgroep. Integendeel. Van het ene moment op het andere bevonden zij zich in een buitengewoon nare en niet te benijden situatie. Dat in zo'n situatie bijna iedereen toestemming geeft om aan onderzoek mee te doen, is verbijsterend. In alle fasen van het onderzoek hebben patiënten en/of hun familieleden op diverse manieren een bijdrage geleverd. Ik dank iedereen meer dan ik kan zeggen. Vanaf deze plaats wens ik ook alle overlevende patiënten en alle familieleden een leven toe, waarbij iedereen een redelijk tot hoog niveau van kwaliteit van leven kan ervaren.
Sommigen schoppen het zelfs tot mede-auteurs en paranimfen: Annelot en Frank, jullie zijn de vertegenwoordigers van die grote groep patiënten en hun familieleden. Wat fijn dat jullie een inhoudelijke bijdrage wilden leveren aan dit proefschrift én mij ook nog terzijde wilden staan bij de verdediging.

Beste Arie, ondanks dat je het nooit hebt uitgesproken, meende ik dat je op het moment dat ik je vroeg om mijn promotor te zijn, nogal sceptisch was. Sceptisch met betrekking tot het onderwerp en de mogelijkheden om überhaupt iets te kunnen zeggen over een behandeleffect. En sceptisch met betrekking tot de haalbaarheid van de promotie. Je koos ervoor om vooral een bijdrage te leveren via de begeleidingscommissie en me nogal mijn gang te laten gaan. Gelukkig maar. Dat paste bij de situatie én bij mijn karakter. Wanneer het nodig was (ik er om vroeg) gaf je je commentaar, dat me altijd aan het denken zette. Mede daardoor is het project goed tot zijn eind gekomen. Ik dank je er hartelijk voor.

Beste Andries, hoewel we al in een vroeg stadium contact met elkaar hebben gehad over onderdelen van de onderzoeksopzet, ben jij pas in een later stadium betrokken geraakt bij dit proefschrift. In ons eerste contact zei je dat dit onderzoek alleen iets kon opleveren als er een controlegroep-onderzoek zou plaatsvinden. Mede op jouw aanwijzingen hebben we dat kunnen doen. Helaas strandde het controlegroep-onderzoek onvoorzien door gebrek aan patiënten. Dat je desondanks promotor wil zijn en zo laat zien dat ook andere onderzoeksvormen een wezenlijke bijdrage aan wetenschap kunnen leveren, waardeer ik zeer.

Beste Paul, jij sprak je twijfels over de haalbaarheid van het project van het begin af aan uit en was toch bereid om mij te helpen en uiteindelijk als co-promotor op te treden. Dat ondanks een geweldig drukke baan, of beter gezegd twee banen. Of misschien wel drie. Onze gezamenlijke bijeenkomsten -vooral in het begin van het traject- stonden vaak onder druk van de tijd en toch bleef je langer zitten dan eigenlijk kon, omdat je het belangrijk vond dat ik geen overhaaste conclusies trok. Steeds opnieuw dwong je me om bij

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mezelf te rade te gaan: waren mijn ideeën en conclusies wel wetenschappelijk onderbouwd? Of liet ik mijn gevoel teveel spreken? Meestal was het terecht dat je me terugfloot. Anderzijds liet je ook steeds weten dat je het onderzoek buitengewoon belangrijk vond en alles op alles wilde zetten om het te laten voltooien. Vooral toen het controlegroeponderzoek een reële mogelijkheid bleek te zijn. Ik ben je heel dankbaar voor je kritische houding en je ondersteuning.

Beste Caroline, jij werd als laatste toegevoegd aan de promotiestaf. "Gelukkig, ook een psycholoog er bij", dacht ik stiekem. Jouw komst was voor dit proefschrift een zeer belangrijke gebeurtenis. Jij was in staat om heel concreet de benodigde hulp te bieden in het, voor mij, moeilijkste deel van promoveren: het schrijven van publicabele artikelen. En niet alleen dat: je hebt zo'n buitengewoon prettige manier om tegen iemand te zeggen dat het toch echt onzin is wat hij heeft geschreven, dat dat mij het gevoel gaf een compliment te krijgen. Die complimenten hielpen mij uit een diepe schrijversput. Mijn berg dank is minstens zo hoog als die put diep was. Ik hoop dat we nog veel kunnen samenwerken.

Dan nu een moeilijk stuk in mijn dankwoord. Ik ben bang dat ik mensen vergeet die op de een of andere manier een bijdrage hebben geleverd aan het onderzoeksproject waar deze promotie uit voortvloeit.
Het project was uniek. In ieder geval in Nederland. We zijn er in 1990 al een klein beetje mee begonnen maar helaas raakten de centen snel op. Als Gerritsen Beheer, in de persoon van oprichter Cees Gerritsen, het in 1997 niet nodig had gevonden ons met een substantieel bedrag te ondersteunen, zou waarschijnlijk in januari 1998, bij de verhuizing van Charlotte Oord naar het Revalidatie Centrum Leijpark (RCL), het doek al gevallen zijn voor het onderzoek en daarmee ook voor het behandelprogramma. In 2004 stond Cees nog eens op de stoep, als een Sinterklaas waar je niet eens voor hoeft te zingen. Cees, ik ben je meer dankbaar dan ik kan zeggen en wens je, nu je je werkzaamheden grotendeels hebt afgebouwd, een geweldig goede tijd samen met Marlies, je steun en toeverlaat.

Geld. Subsidie. Fondsen. Een van de grootste problemen bij elk onderzoek (dat niet binnen een groot project vanuit een universitair centrum wordt uitgevoerd). Ik heb er een paar grijze haren aan over gehouden (zie baard). Gelukkig waren er de Stichting Centraal Fonds RVVZ, het Johanna Kinderfonds, de CZ Groep Zorgverzekeringen Fonds vrijwillige verzekeringen, de Zorgverzekeraar VGZ Fonds vrijwillige verzekeringen, Zorg en zekerheid, de Stichting Bio Kinder-revalidatie en de Hersenstichting Nederland. Al deze fondsen hebben in de loop der tijd substantiële bijdragen geleverd, aanvullend op die van Cees Gerritsen. Onmisbaar om het onderzoek zo lang te kunnen uitvoeren.
Hartelijk dank aan de fondsen en in het bijzonder aan hun vertegenwoordigers.

Dankwoord

De directie van Charlotte Oord / raad van bestuur van RC Leijpark en het management van beide instellingen ben ik dankbaar voor de ruimte en steun die ik heb gekregen om het project vorm te geven en uit te voeren, en daarbij het promotietraject te volgen en af te ronden, ook al duurde het veel langer dan gepland.

Annemiek de Kock en Esmée Verwijk hebben een cruciale rol gespeeld in het ontwikkelen en deels uittesten van de onderzoeksopzet, die uiteindelijk in 1998 werd ingevuld. Jullie betrokkenheid, creativiteit en enthousiasme én jullie vriendschappelijkheid hebben mij enorm geholpen om door te zetten met het zoeken van fondsen en het oplossen van complexe methodologische vraagstukken. Annemiek en Esmée weten allang hoe dankbaar ik hen ben: nu weet iedereen het.

Aan het onderzoeksproject zelf hebben heel veel mensen hun medewerking verleend. Teamleden, verpleging, secretariaat, technische dienst, kopieermedewerkers, medisch-ethische commissies, artsen en verpleegkundigen uit andere ziekenhuizen, enz. enz.
Het is niet mogelijk alle namen te noemen, al ben ik iedereen meer dan dankbaar voor de inzet voor dit onderzoek. Vooruit: een paar mensen wil ik er uit lichten. Niek van Haasteren, Ine Bongenaar, en Annemiek Klessens hebben meegedacht en (de laatste twee) vooral in het prospectieve onderzoeksdeel stapels scoreformulieren met gegevens aangeleverd, die de basis vormen voor de gevonden resultaten.

De uitvoering van alle onderzoeksdelen kon ik niet alleen. Veel mensen hebben meegedaan. Ik wil alle collega's die als onderzoeker, als onderzoeksmedewerker of als onderzoeksstagiaire een bijdrage hebben geleverd vanaf deze plek nog een keer heel hartelijk danken. Margot (als eerste, al in 1988), Marleen, Margé, Anjo, Debby, Sylvia, Yvonne, Neeltje, Hanneke, Geert, Susan, Raisy, Angela, Véronique, Maartje, Willem, Eefje, Janine, Marijn, en in het bijzonder Viona Wijnen (als mede-onderzoeker, die ook de 'geneugten' van het schrijven van een proefschrift en het promoveren kent) en Matagne Heutink (volstrekt onmisbaar als onderzoeks-medewerker die oog heeft voor ALLE details, en meer dan dat): dank je, dank je, dank je wel.
Wat heeft ieder van jullie op haar of zijn manier geweldig meegedaan aan dataverzameling (waaronder lange ritjes naar verre ziekenhuizen), dataverwerking en het schrijven van het eindverslag en artikelen.

Niet onvermeld mag blijven de steun die tussen de regels door werd verleend ten behoeve van de methodologie en statistiek. Jan Schiers van de Universiteit van Tilburg (UvT) stond met zijn rustige en vriendelijke benadering altijd klaar om vragen te beantwoorden. Die lang niet altijd alleen over methodologie en statistiek gingen, trouwens. Geweldig, Jan. Jouw bijdrage was mogelijk, omdat Ton Heinen bereid was een samenwerkings-

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overeenkomst tussen UvT en RCL aan te gaan. Ton: bedankt. Viona en ik hebben er veel aan gehad.

Jennifer, the corrections you made in my manuscripts, filled with strange and silly English sentences, were crucial for accepting the articles. Well done and thank you.

Ieder goed onderzoeksproject kent een begeleidingscommissie. De leden van 'onze' commissie: Harrie van Daal, Pauline Hoenderdaal, Andrew Maas, Arie Prevo, Hans Stroink, Ad Vingerhoets en Harry van der Vlugt dank ik bijzonder voor hun deskundig commentaar in allerlei fases van het onderzoeksproject. Jullie hebben sturing gegeven op momenten dat we de weg zochten. Pauline was zelfs genegen om een actieve rol te spelen bij de beoordeling van 44 video-opnames, waardoor we een belangrijke stap konden maken in de validering van de PALOC-s.

Eén lid van de begeleidingscommissie dank ik in het bijzonder: Jan Lavrijsen. Jouw bijdrage is veel meer geweest dan sturing. Ook jij deed mee aan de validering van de PALOC-s. Jij betrok mij actief bij jouw eigen promotieonderzoek. Samen bezochten we, als vertegenwoordigers van Nederland binnen dit veld, enkele internationale congressen. Leerzaam én gezellig.
En jouw enthousiasme om bij de doelgroep goed onderzoek te doen, jouw intense betrokkenheid met de problematiek én de creatieve manier waarop je zelfs de Paus, zowel letterlijk als figuurlijk, onder de duim wist te houden hebben mij enorm gestimuleerd.
En dat niet alleen: je bent ook gewoon een goeie vriend.

Het is de gewoonte om aan het eind van een dankwoord de naaste gezinsleden te danken. Hoewel het niet mijn gewoonte is om met gewoontes mee te doen, is dat zeker op zijn plaats.
Lieve Mick, ook al zei je dat ik het uit mijn hoofd moest laten om jou te bedanken, doe ik dat toch (tja, een beetje eigenwijs, hè!).
Op sommige momenten heb je meer mijn rug gezien -als ik weer eens een avond aan de PC zat- dan iets anders. Of misschien moet ik wel zeggen: heel vaak heb je …...
Na meer dan 40 jaar weet je wel hoe ik in elkaar steek en ook dat het vaak niet anders kon.
Je was ook niet te beroerd om op de een of andere manier te ondersteunen, of vakanties op te schuiven, of weer eens aan avond alleen te eten als ik ergens naar toe moest. Totdat het tijd werd om even een knop om te draaien: dan liet je het ook horen.
Nu mijn promotie achter de rug is, zal ik meer tijd krijgen om samen dingen te doen. Wat dat zal zijn, zien we wel. We hebben interesses en ideeën genoeg.
Ik kijk er naar uit.

Curriculum Vitae
en
publicatielijst

CV en publicatielijst

Curriculum Vitae

Henk Eilander is op 12 december 1947 geboren in Hengelo (O). Hij ging na de HBS-b in 1965 in Groningen wis- en natuurkunde studeren. Dat bleek al snel geen succes. Na een college van Wilhelmina Bladergroen te hebben gehoord raakte hij voorgoed gefascineerd door kinderen met een ontwikkelingsprobleem. Henk studeerde in 1972 af in de ontwikkelingspsychologie, met als nevenvak neuropsychologie.
Na het uitvoeren van vervangende dienstplicht in een instelling voor verstandelijk gehandicapten heeft hij van 1975 tot 1981 in een vergelijkbare instelling in Zuid-Limburg gewerkt als psycholoog. Daar kwam hij in aanraking met mensen met niet-aangeboren hersenletsel en met het Revalidatiecentrum Hoensbroeck. De interesse in behandelen leidde in 1981 tot een overstap naar het kinderrevalidatiecentrum Charlotte Oord in Tilburg. Daar heeft Henk gewerkt met kinderen van 0 tot 20 jaar, met een progressieve of regressieve aandoening, klinisch opgenomen of in een eenmalig consult. En alles daar tussen in. Halverwege de jaren '80 nam de problematiek van kinderen met niet-aangeboren hersenletsel (NAH) een steeds grotere plaats in in zijn werk. Vanaf 1987-1989 heeft Henk opnieuw een doctoraal programma in de psychologie gevolgd en afgerond: ditmaal in de neuropsychologie in Tilburg.
Henk was in Charlotte Oord hoofd van de agogische dienst van 1983 t/m 1994. Toen de organisatie werd gekanteld werd hij behandelteamcoördinator van het NAH-team.

In 1987 was Henk één van de mensen die het 'stimuleringsprogramma coma-patiënten' (nu dus het behandelprogramma Vroege Intensieve Neurorevalidatie) hielp opzetten. Toen al snel duidelijk werd dat het belangrijk was om het programma systematisch te evalueren heeft hij daartoe het initiatief genomen, wat uiteindelijk heeft geleid tot dit proefschrift. Vanaf april 1999 is hij full-time bezig geweest met het onderzoek naar het effect van het VIN-programma: deels als projectleider, deels als onderzoeker.

Henk is bestuurlijk actief geweest in de Comavereniging Nederland en in de sectie Revalidatie van het Nederlands Instituut van Psychologen (NIP). Daarnaast nam of neemt hij deel aan diverse landelijke of provinciale commissies op het gebied van niet-aangeboren hersenletsel.
Henk heeft meerdere publicaties op zijn naam, zowel populairwetenschappelijk, als op zijn vakgebied.
Hij geeft regelmatig les en levert bijdragen aan symposia en congressen.

In zijn (schaarse) vrije tijd behoort het onderhoud van een moestuin of het leveren van een sportieve prestatie tot de favoriete bezigheden, maar ook fotografie en (digitale) vormgeving hebben zijn interesse.

Henk is getrouwd met Mick (sinds 1969), zij hebben één zoon.

CV en publicatielijst

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