Overcoming the Odds

Long-term psychosocial outcomes in survivors of meningococcal septic shock in childhood, and in their parents

Lindy Vermunt

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Denyse Kats

Aan mijn ouders

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1 General Introduction

General Introduction

Meningococcal septic shock

Invasive meningococcal disease (MD) is classified as meningitis, sepsis, septic shock or a combination of meningitis with sepsis or septic shock. The most severe cases develop septic shock. Septic shock with petechiae and/or purpura is caused mainly by *Neisseria meningitidis* and is also called Meningococcal Septic Shock (MSS). MSS is the most severe form of meningococcal infection in early childhood because of the rapid progress of the clinical picture and the deterioration of the cardiovascular system resulting in a high morbidity and mortality. MSS is often confused with meningitis, patients with septic shock show the clinical features of meningitis but in addition the cardiovascular collapse of a septic shock causes a more fulminant illness with a higher mortality rate.

MSS causes a life-threatening illness in mostly previously healthy children with an unexpected and sudden onset. After onset, it progresses fulminantly, requiring admission to a Paediatric Intensive Care Unit (PICU). Children with MSS are one of the most severely ill and unstable groups of children admitted to a PICU. A previously healthy child may die within 24 hours.

Neisseria meningitidis (the meningococcus) is a Gram-negative diplococcus. This organism is transmitted by contact with respiratory secretions. The disease occurs when the organism penetrates a mucosal surface and is transported in the blood stream by leucocytes. Infection then localises in organs such as the lungs, joints, meninges, heart, eyes and adrenal glands. The bacterial endotoxin sets up a complex cascade of events resulting in complement activation, diffuse vasculitis, disseminated intravascular coagulation, shock and multiple organ damage (Belthur et al., 2005). Despite advances in treatment, mortality and morbidity remain high (19% Baines & Hart, 2003; 15.7% Maat et al., 2007). The incidence of meningococcal septicaemia is highest among young children (< 4 years) and teenagers, and it occurs in 4.5 per 100,000 inhabitants of The Netherlands (Hazelzet, 2005). Meningococcal disease is more commonly seen in areas with low socio-economic status (Stuart et al., 2002).

Physical elements of MSS

There are certain disease-specific elements of MSS that make this syndrome very unique. The illness develops very suddenly and fulminantly. After the first symptoms (e.g. high fever, petechiae) have appeared, physical functioning rapidly deteriorates and consequently causes the patient to develop shock, disseminated intravascular coagulation (DIC) and ultimately organ failure. Impaired nervous system function may be seen in meningococcal disease as a result of both direct invasion of the meninges by the brain and as part of the organ under perfusion and microvascular obstruction in septic shock. Profoundly shocked patients invariably show diminished consciousness and are at risk of cerebral infarction if perfusion is not improved (Pathan et al., 2003). MSS may also result in somatic sequelae like scars, amputation(s) of digit(s) as a result of skin necrosis, and limited motor functioning because of orthopedic sequelae and amputations.

It is assumed that children who survive the acute phase of the disease may be at risk for cognitive impairment, organ damage, loss of hearing, and body disfigurement.

Psychological elements of MSS

Next to the biological impact that the illness causes, there is also an immense emotional impact of the acute MSS. Children become suddenly very ill and are admitted to a PICU, where they are exposed to invasive procedures. This is an extremely stressful event that has an overwhelming impact on both parents and children. A PICU admission causes a wide range of negative emotions in children and is often traumatic for them (Rennick et al., 2002; Cooper, 2006). For parents, living through this experience is perceived as a major stressor (Haines, 2005). In the first critical period, parents experience extreme fear of a possible death. Thereafter, uncertainties about long-term consequences, e.g. due to possible physical sequelae, arise. It is assumed that psychosocial consequences may encompass cognitive dysfunctioning, behavioural and emotional problems, including post-traumatic stress problems, and self-esteem problems in children who survived MSS and psychosocial problems in young adult survivors as well as the parents. Until now little is known about psychosocial aspects of having survived MSS in childhood. There has been no systematic research on physical and psychosocial outcome of a homogeneous sample of MSS children.

Cognitive functioning in children and adolescents who survived septic shock

The major pathophysiological event occurring in MSS is related to an impairment of micro vascular blood flow to the tissues and organs as a result of shock and disseminated intravascular coagulation. Impaired central nervous system function may also be seen in MSS as a result of direct invasion of the meninges by the bacteria (meningitis) or cerebral oedema. Reduced perfusion of the brain, caused by shock and micro vascular thrombi may lead to cerebral ischemia. A high proportion of abnormal brain imaging was found in septic shock in adults in a recent study by Sharshar et al. (2007). The possible effects of MSS on cognitive functioning have not been investigated before, however. Only one study focussed on long-term cognitive functioning in children who survived MD (Fellick et al., 2001). In this study it was found that 115 patients aged 8-25 years performed at a lower level than a comparison group on measures of cognition and behaviour, 8-12 years after MD. Children who survived MD obtained lower scores on total IQ, Performal IQ and Verbal IQ and on visual-motor integration. On total IQ MD survivors obtained scores that were 6.4 points lower than a comparison group. A review and a few other studies focussed on cognitive outcome after bacterial meningitis (Taylor et al., 2000; Fellick & Thomson, 2002; Anderson et al., 2004). Poorer cognitive functioning was found in children with bacterial meningitis versus a comparison group. Predictor variables that were identified in the above studies were: presence of seizures, low serum glucose level at time of acute illness and younger age at time of illness (Grimwood, et al., 1996; Anderson, et al., 1997; Taylor et al., 2000; Koomen et al., 2004; Anderson et al., 2004). However, meningitis and MSS have very different pathophysiologies and are therefore difficult to compare. Data as to cognitive outcome of MSS specifically, and its predictors, are lacking.

Behavioural and emotional problems, including post-traumatic stress problems in children and adolescents who survived septic shock

The PICU admission can be traumatic for children as they are separated from their families and security of their own home (Cooper, 2006). Children have been observed to demonstrate anxious, withdrawn, fearful, restless, angry or hostile behaviour during their PICU hospitalization (Rennick et al., 2002). Children who are discharged from the PICU are at risk for 'the vulnerable child syndrome', which indicates that their parents may subject the child to overprotective parenting (Youngblut & Schiao, 1993). Parents may have difficulty setting limits and may become overly indulgent. This might result in children who are overly dependent, immature and non-compliant. Overall, the biological and emotional stress imposed by MSS and in addition the PICU admission may place children at risk for negative psychological outcomes.

Three studies investigated emotional functioning in children who survived MD, focussing on short-term outcomes. In these studies high rates of psychiatric disorders were found (Judge et al., 2002; Shears et al., 2005; Shears et al., 2007). Only one study investigated the long-term behavioural outcomes of MD, using one questionnaire with scales that were designed to assess Attention Deficit Hyperactivity Disorder (ADHD) and related behavioural problems (Fellick et al., 2001). In this study it was found that at 10-year follow-up, parents and teachers reported significantly more cognitive- and global problems and ADHD symptoms for ex-patients compared to parents and teachers of a comparison group. However, no study has yet focussed on behavioural and emotional problems, including post-traumatic stress problems, after MSS specifically.

Self-esteem in children and adolescents who survived septic shock

Impairments of MSS as to motor functioning, due to orthopedic sequelae and amputations, and physical appearance, due to scars, can have a negative influence on the self-esteem of child- and adolescent-survivors of MSS. Self-esteem is the evaluation of the self concept. It is defined as the total of ideas and notions that a person has about herself or himself (Harter, 1988).

Only one, small qualitative study has focused on self-esteem in children who survived meningococcal septicaemia (Wallace et al., 2007). Eleven adolescents aged 13-25 years were interviewed 1 to 7 years after MS. Despite the impact the illness had on their lives and their altered appearance, the adolescents showed a high degree of resilience in reaction to their experience. Self-esteem has not been investigated systematically in a large sample of MSS survivors before. Since no previous data are available to compare with, a brief review of studies into psychological outcome in burn-survivors scars is given below. Self-esteem of children and adolescents who have been burned has been investigated by several authors. Le Doux et al. (1996) found higher self-esteem in children who were 10%-67% burned, 2 years after the traumatic event, compared to a healthy reference group. Children and adolescents who were burned demonstrated a better self-esteem in the areas of social acceptance. Adolescents further described themselves as having greater romantic appeal whereas children reported higher estimates of global self-esteem. Two years post-burn, Robert et al. (1999) found similar or higher levels of self-esteem in 13-20 year old children who had scars in at least two areas of the body compared to 'normal' peers. Athletic competence and physical appearance were significantly lower in these children compared to a comparison group. In a recent study positive general feelings about their appearance were found in 36 adolescents, aged 11-19, who were burned as children (Pope et al., 2007). The conclusion of this study seems to be applicable to all the above studies: young burn survivors appear to be doing well in comparison to their peers, and in some areas even better, in spite of living with the physical, psychological and social consequences of burns. The relation between the presence of scars, the evaluation of scars and self-esteem has not been investigated in MSS survivors.

Psychosocial functioning in adult survivors of septic shock in childhood

Psychosocial functioning in adults, who survived MSS in childhood, has not been investigated before. One study focussed on young adults who survived MD (Fellick et al., 2001). This study described neurodevelopmental outcome in 8-25 year old patients who survived MD, 8-12 years after the illness. Fellick et al. concluded that the majority of patients had no gross neurological deficits, sequelae as to motor function, cognitive function and behaviour.

Nothing is known about psychosocial outcome of adult MSS survivors. The present study will give insight in the psychosocial functioning of adults who survived MSS, including psychosocial, behavioural and emotional, and intellectual functioning.

Psychosocial functioning in parents of children who survived septic shock

Haines (2005) concluded that for parents the experience of meningococcal disease in their child is a major stressor. She found that the transition from the role of 'parent of a healthy child' to 'parent of a critically ill child', next to feelings of helplessness and guilt were major sources of stress. Parents may be extremely emotional, feel vulnerable and may disbelieve what is happening. Fear about a possible death and uncertainties about possible physical or mental consequences for their child after survival, elevates their stress and anxiety levels. Parents are often overwhelmed and shocked by the invasive treatment measures and the changed appearance of their child is very upsetting. In a recent review it was found that PICU admission of a child imposes severe stressors on families (Shudy et al., 2006). It may be clear that when a child gets MSS, the most severe form of meningococcal disease, it places an even more immense burden on the child and its parents (Haines, 2005).

A few studies have investigated the short-term psychological consequences for parents of children who survived MD. Symptoms of post-traumatic stress disorder (PTSD) were found in 48% of mothers and risk for high levels of psychological distress in 40-43% of mothers, 3 to 12 months after admission for MD (Judge et al., 2002; Shears et al., 2005). In 19% of fathers high risk for post-traumatic stress disorder was found and in 24% high levels of psychological distress, 3-12 months after MD in their child (Shears et al., 2005). High rates of post-traumatic stress, acute stress and psychological distress were also found in parents 2 to 12 months after their child was admitted to a PICU (Board & Ryan-Wenger, 2002; Rees et al., 2004; Ballufi et al., 2004; Colville & Gracey, 2006). Only one study investigated long-term consequences of MD in parents. In this study, using five small cross-sectional subgroups of patients assessed at different time-intervals (3 months up to 36 months or longer after discharge from the PICU), Ehrlich et al. (2005) found a prevalence of psychological distress in mothers and fathers comparable to that in the general population, 3 years or more after discharge. All the above studies encompassed parents of heterogeneous samples of children who survived MD. Studies in which long-term psychosocial outcome is investigated in parents of homogeneous samples of MSS survivors, are lacking.

The present study: a long-term follow-up

The objective of the study was to assess in a large sample (6-31 years old) the long-term outcomes of having survived septic shock caused by *Neisseria Meningitidis* in childhood. Outcomes were both from a medical and psychosocial point of view. The focus of the study described in this thesis is on the psychosocial outcomes. Various indicators of the psychosocial functioning of children and adolescents who survived MSS were measured, including intellectual and neuropsychological functioning, behavioural and emotional problems, including post-traumatic stress problems, and self-esteem. For young adults who survived MSS in their childhood the following indicators for psychosocial functioning were measured: biographical characteristics, disease-specific consequences, behavioural and emotional problems and intellectual functioning. Also, the psychosocial functioning of parents was examined, with the focus on mental health and disease-specific psychosocial limitations. Outcomes on the various indicators of psychosocial functioning for the patient sample were compared with those in the general population. The role of age and gender was systematically examined. Furthermore, the predictive value of severity of illness and age at time of illness was examined. The predictive value of a broader range of medical variables on intellectual and neuropsychological functioning of MSS child survivors was also examined.

The aim of the present study was to investigate the long-term psychosocial outcomes of children, adolescents and young adults who survived septic shock, caused by *Neisseria meningitidis* in childhood, and their parents. The specific aims hereby were:

1. To compare the present psychosocial functioning, encompassing intellectual and neuropsychological functioning, behavioural and emotional problems, including post-traumatic stress problems, and self-esteem, of children and adolescents, and psychosocial functioning of young adults, who survived MSS, with that of normative samples.
2. To compare the present psychosocial functioning of both mothers and fathers of the patient sample with those of normative samples.
3. To determine the role of age at time of follow-up and gender on psychosocial functioning.
4. To examine the predictive value of age at time of illness, severity of illness and other medical variables on psychosocial functioning of the patient sample.

Methods

Inclusion criteria

During the follow-up, which took place in 2005-2006, all consecutive surviving patients with a clinical picture of meningococcal septic shock, defined as septic shock with petechiae/purpura, requiring intensive care treatment at the PICU of ErasmusMC-Sophia Children's Hospital at least 4 years ago (between 1 August 1988 and 1 June 2001) were eligible. In 84% of the patients *Neisseria meningitidis* was cultured. Parents and patients who were not Dutch speaking were excluded.

Patient sample

The target population consisted of 179 consecutive surviving patients. At follow-up 9 patients were lost (7 moved abroad, 1 was untraceable, 1 was deceased). Of the remaining 170 patients, 34 refused to participate. The present patient sample consisted of the remaining 136 patients (mean age: 15.03, age range 6-31 years) of which 67 were males and 69 were females. The overall response rate was 80.0%. Results of all participating patients were included in this thesis. Patients were 6-31 years old at time of follow-up, with a follow-up interval of 4 to 16 years.

Since the instruments used to assess various indicators of psychosocial functioning did not cover the same age-ranges, the numbers of patients and parents in the chapters 2 to 7 of this thesis differ. The exact numbers and response rates are indicated in the corresponding chapters.

Psychosocial instruments

In selecting assessment instruments we chose to use Dutch translations of internationally well-known instruments of which the psychometric properties (validity, reliability) are satisfactory (see table 1).

For the children and adolescents the following tests and questionnaires were used. *Cognitive functioning* was assessed with the Dutch versions of the Wechsler Intelligence Scale for Children III (WISC-III), the Stroop Color Word Test, the Trail Making Test part A and part B, the subtest 'Score!' of the TEA-Ch, the Beery VMI, the 15- Word Test and long-term 15-Word Test (Saan & Deelman, 1986; Wechsler, 1991; Beery, 1997; Manly, 1999; Kort et al., 2002; Lezak, 2004). *Behavioural, emotional and post-traumatic stress problems* were assessed with the Child Behavior Checklist (CBCL), the Youth Self-Report (YSR) and the Teacher's Report Form (TRF) (Achenbach & Rescorla, 2001). *Self-esteem* was assessed with the Dutch versions of Harter's Self-Perception Profile for Children (SPP-C; Veerman et al., 1997) and Harter's Self-Perception

Table 1. Psychosocial assessment instruments for child, adolescent and adult MSS survivors, and their parents.

	Children and adolescents	Adults	Parents
Cognitive functioning	• Wechsler Intelligence Scale for Children III (WISC-III) • Stroop Color Word Test • Trail Making Test part A and B • subtest 'Score!' of the Test of Everyday Attention for Children (TEA-Ch) • Beery VMI • 15 Word Test and long-term 15 Word Test	• Groninger Intelligence Test 2 (GIT2)	-
Behavioural and emotional problems (including post-traumatic stress problems*)	• Child Behavior Checklist (CBCL) • Youth Self-Report (YSR) • Teacher's Report Form (TRF)	• Adult Self-Report (ASR)	-
Self-esteem	• Self-Perception Profile for Children (SPP-C) • Self-Perception Profile for Adolescents (SPP-A) • Patient Scar Assessment Scale (PSAS)	-	-
Biographical characteristics and disease-specific consequences	-	• Semi-structured interview	• Semi-structured interview
Mental health	-	-	• General Health Questionnaire (GHQ-28)

* Post-traumatic stress problems were assessed only in the child and adolescent sample

Profile for Adolescents (SPP-A; Treffers et al, 2002). *Scar severity* was assessed by means of the Patient Scar Assessment Scale (PSAS; Draaijers et al., 2004).

Instruments for young adult MSS survivors: to assess *biographical variables and disease-specific consequences* a semi-structured interview was performed. *Intellectual functioning* was assessed with the Groninger Intelligence Test 2 (GIT2; Luteijn & Barolds, 2004). *Behavioural and emotional problems* were assessed with the Adult Self-Report (ASR; Achenbach & Rescorla, 2003).

Regarding the parents the following instruments were used: to assess *biographical variables and disease-specific consequences* a semi-structured interview was performed with the parents. *Mental health* of parents was assessed with the General Health Questionnaire (GHQ-28; Koeter & Ormel, 1992).

Severity of illness

The following three classifications for severity of illness were used in the present study: the Paediatric Risk of Mortality Score (PRISM), based on the most abnormal values for physiological variables, the Vasopressor score (VAS), indicating type and dose of vasopressors/inotropes, and the Disseminated Intravascular Coagulation score, indicating severity of disseminated intravascular coagulation (Pollack et al., 1988; Wernovsky et al., 1995; Taylor et al., 2001).

Assessment procedure

The research protocol was approved by the ethics committee review board. All parents and their children were traced, approached uniformly and signed an informed consent. During their visit to the ErasmusMC-Sophia Children's Hospital, all patients were interviewed and tested by the same psychologist (LV) and medically examined by a paediatric intensivist (CB). Some patients, who could not visit the hospital for practical or emotional reasons, completed the questionnaires at home and returned them with a prepaid envelope. The CBCL, YSR and ASR questionnaires were sent to patients and their parents to be filled in at home and taken with them to the psychological investigation. Parents of patients completed the questionnaires, independently of each other, in the waiting room. They were also asked to deliver a questionnaire to the teacher, who could return it with a prepaid envelope. Parents were interviewed after the psychological examination of their child.

The structure of this thesis

After this introduction in **chapter 1**, in **chapter 2** the levels of intellectual and neuropsychological functioning in children and adolescents from the patient sample are examined. In addition predictor variables are identified. In **chapter 3**, the occurrence of a wide range of behavioural and emotional problems in children and adolescent MSS survivors is assessed.

The level of post-traumatic stress problems is also investigated. In **chapter 4** the focus is on self-esteem and its relation to scars, amputations and orthopedic sequelae in children and adolescents from the patient sample. In **chapter 5** the focus is on young adult MSS survivors and their psychosocial functioning long-term after MSS. **Chapter 6** focuses on mental health and disease-specific psychosocial limitations in both mothers and fathers of children and adolescents from the present patient sample. Finally, in **chapter 7**, the main findings and conclusions of this thesis are discussed. Implications and recommendations for medical practice are given.

3

Behavioural, emotional and post-traumatic stress problems in children and adolescents long-term after septic shock caused by *Neisseria meningitidis*

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Abstract

Aims

To assess the occurrence of a wide range of behavioural, emotional and post-traumatic stress problems in children and adolescents, long-term after septic shock caused by *Neisseria meningitidis* (MSS).

Methods

Included were 6-17 year old patients who survived MSS and were admitted to the PICU of the Medical Centre between 1988 and 2001. To assess behavioural, emotional and post-traumatic stress problems the Child Behavior Checklist (CBCL), the Teacher's Report Form (TRF) and the Youth Self Report (YSR) were used. Parents of 89 MSS children, aged 6-17 years, completed the CBCL. Teachers of 65 children same-aged MSS children completed the TRF and 45 11-17-year-old MSS children completed the YSR. These data were compared with those from normative reference groups.

Results

Overall, the proportions of MSS children scoring in the deviant range for problem behaviour were comparable to the proportions in the reference groups, according to parents', teachers' and self-reports.

As to the level of emotional and behaviour problems, mothers of MSS children reported more somatic complaints regarding their children in comparison with the reference groups.

Severity of illness was not a significant predictor of behavioural, emotional and post-traumatic stress problems. Age at time of illness was a significant predictor of behavioural, emotional and post-traumatic stress problems in MSS children, indicating that the younger the child at time of illness, the more problems were reported by parents at follow-up.

Conclusion

Overall, the results showed long-term behavioural, emotional and post-traumatic stress outcomes for MSS children, which were comparable to those in the general population.

Introduction

Septic shock in children and adolescents caused by *Neisseria meningitidis* is a life-threatening illness that has an abrupt onset and a fulminant course. Despite advances in knowledge about pathophysiology and treatment, morbidity and mortality remain high (19%; Baines & Hart, 2003). Because of the severe, rapid progression of this disease the child with Meningococcal Septic Shock (MSS) is admitted to a Paediatric Intensive Care Unit (PICU). Children with MSS are one of the most severely ill and unstable groups of children admitted to a PICU. A previously healthy child may die within 24 hours. The acute disease of MSS exposes both children and parents to an overwhelming amount of emotional distress and has a profound emotional impact on them.

Little is known about psychological consequences of MSS. A few studies have investigated the short-term psychological consequences of MSS in surviving children. Shears et al. (2005) found symptoms of post-traumatic stress disorder in 15% of 26 children with meningococcal disease, at a 3-month follow-up. Judge et al. (2002) found post-traumatic stress symptoms in 62% of 29 children with meningococcal disease, 3-12 months after the disease. Shears et al. (2007) found psychiatric disorders in 32% of 40 children with meningococcal disease at 12-month follow-up; in 2% of these 40 children post-traumatic stress disorder was found. Only one study has investigated the long-term behavioural consequences of meningococcal disease. In a heterogeneous sample of patients with meningococcal infection, Fellick et al. (2001) found poorer functioning on measures of coordination, cognition and behaviour than in a comparison group, 8-10 years after the disease.

Most previous studies mentioned above focused on short-term consequences and/or used small, heterogeneous samples, consisting of children with meningitis, septicaemia or mixed disease. In our study, however, we focused on long-term consequences in a large *homogeneous* sample, consisting of only children and adolescents who survived septic shock caused by *Neisseria meningitidis*. Moreover we used four different informants (mother, father, teacher and children themselves), while all other studies used only 1 or 2 informants. As far as we know, until now no study has investigated systematically the long-term behavioural, emotional and post-traumatic stress problems in these patients before. The aims of the present study were:

1. To compare the level of behavioural, emotional and post-traumatic stress problems in children and adolescents who survived septic shock caused by *Neisseria meningitidis* with that of same-aged reference groups.
2. To identify the role of gender, age at the time of follow-up, age at time of illness and severity of disease on the level of behavioural, emotional and post-traumatic stress problems.
3. To determine the discrepancies between child and parent ratings and between parent and teacher ratings within this sample of patients.

Methods

Instruments

Child Behavior Checklist (CBCL), Teacher's Report Form (TRF) and Youth Self-Report (YSR)

The Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001) was used to obtain standardized parents' reports of behavioural and emotional problems in children aged 6-17 years. The problem section consists of 120 problem items. Parents rate their child's behaviour during the preceding six months on a 3-point scale (0 = not true; 1 = somewhat or sometimes true; 2 = very true or often true).

For the same age-category (6-17 years old) of children and adolescents, the Teacher's Report Form (TRF)(Achenbach & Rescorla, 2001) was used to obtain reports of behavioural and emotional problems from teachers. The TRF parallels the CBCL and assesses the child's behaviour in the past 2 months.

For 11-17-year-olds the Youth Self-Report (YSR) (Achenbach & Rescorla, 2001) was used to obtain adolescents' self-reports. The YSR was modelled after the CBCL and has the same format, except that items are worded in the first person.

Good validity and reliability of the CBCL, TRF and YSR have been established (Achenbach & Rescorla, 2001) and were confirmed for the Dutch translations (Verhulst et al., 1996, 1997a, 1997b)

All three questionnaires consist of 8 specific syndrome scales and two broad problem areas: Internalizing (Withdrawn, Somatic Complaints and Anxious/Depressed) and Externalizing (Rule-Breaking and Aggressive Behaviour)(see Table 1). A Total Problem score can be obtained by summing the scores on all individual problem items. A higher score indicates a higher level of problems.

Posttraumatic Stress Problems scale (PTSP)

The Posttraumatic Stress Problems scale (PTSP) assesses problems that researchers on posttraumatic stress have identified and validated as being significantly associated with experiences of traumatic stress (Achenbach & Rescorla, 2007). This PTSP scale consists of 14 items from the YSR, the TRF and from the CBCL. Good reliability (r = 0.83 - 0.88) and moderately high internal consistency (alpha = 0.74 - 0.75) have been reported for the PTSP (Achenbach & Rescorla, 2007).

PRISM-score

The Paediatric Risk of Mortality (PRISM) score, a validated score, was used as index of severity of illness (Pollack et al., 1988). The score is calculated on the basis of the most abnormal values for physiological variables during the first 24 hours of admission to an Intensive Care Unit.

Semi-structured interview

A semi-structured interview with parents was performed to assess biographical variables, to get an impression of subjective experiences of the children and their parents and to investigate the 'medical consumption' of the children at time of follow-up. 'Medical consumption' included contacts with professionals from mental health care services (e.g. social worker, psychologist, psychiatrist) for behavioural or emotional problems of patients.

Description of the samples

Inclusion and exclusion criteria

The follow-up took place in 2005-2006. Eligible were consecutive surviving patients with a clinical picture of meningococcal septic shock (MSS), who required intensive care treatment at the PICU of ErasmusMC-Sophia Children's Hospital at least four years ago (between 1 August 1988 and 1 June 2001). In this study MSS is defined as septic shock with petechiae/purpura. For a detailed description of septic shock see Joosten et al. (2000). In 83% of the patients *Neisseria meningitidis* was cultured. Parents and patients who were not Dutch speaking were excluded.

For the present study, parents and teachers of 6 to 17 year-old children and children aged 11 to 17 years were included. This was the first long-term follow-up study conducted with these patients.

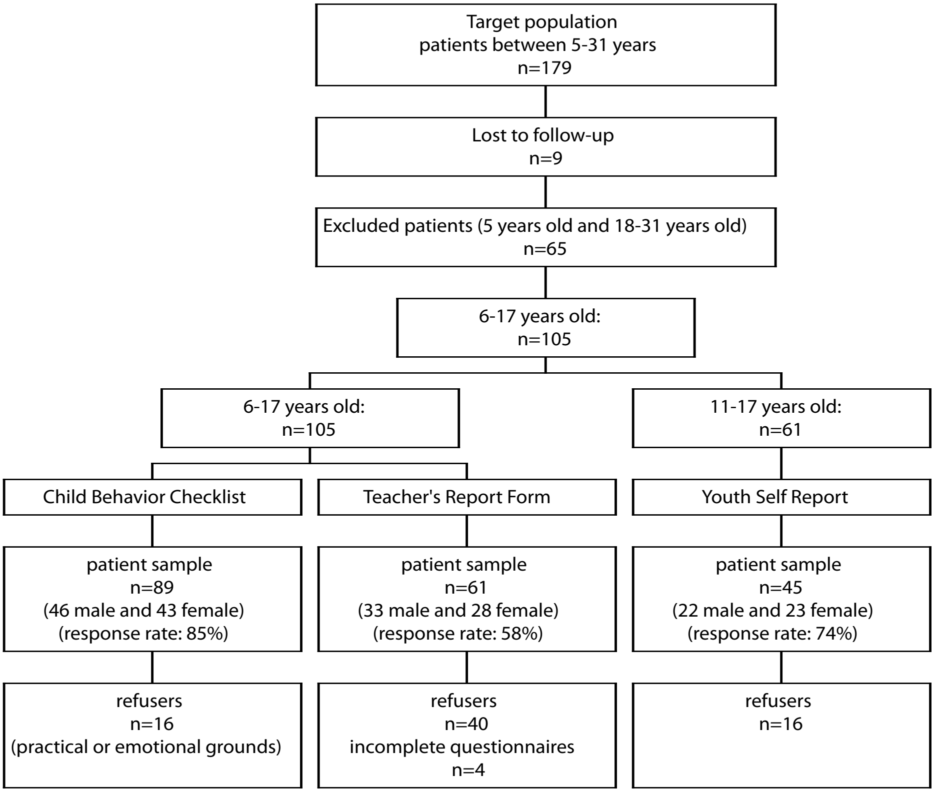
Sample of patients

In figure 1 the patient flow chart is presented. For non-responding parents and teachers the mean age of patients (parents sample: 14 years, teachers sample: 13 years) was significantly higher than the mean age of patients whose parents and teachers did participate in this study (parents sample: 11 years, teachers sample: 10 years). Statistical tests showed that non-responding patients were significantly older at follow-up and significantly more ill at time of MSS than responding patients. The non-responding patients contained significantly more boys compared to the responding patients.

The sub samples of the present study partly overlapped since the CBCL, TRF and YSR partly covered the same age-ranges. The final study samples (see figure 1) consisted of the following sub samples:

1. *CBCL sample of patients.* For 75 children the CBCL was completed by both mothers and fathers. For 11 children only mothers filled in the CBCL and for 3 children only fathers filled in the CBCL.
2. *TRF sample of patients.*
3. *CBCL-TRF overlapping sample.* For 58 children both a CBCL questionnaire filled in by mother and a TRF questionnaire filled in by the teacher were available. For 54 children a

Figure 1. Inclusion of patients



CBCL questionnaire filled in by father as well as a TRF filled in by the teacher were available.

4. *YSR sample of patients.*
5. *CBCL-YSR overlapping sample.* For 44 children both a CBCL filled in by mother and an YSR were completed. For 38 children a CBCL questionnaire filled in by father as well as an YSR questionnaire filled in by a MSS child were available.

Reference groups

CBCL, TRF and YSR scores for patients were compared with scores derived from representative Dutch samples from the general population, with comparable age-ranges assessed (Tick et al., 2008). These normative data were gathered from December 2003 till April 2005.

1. CBCL reference group: parents of 760 boys and 779 girls, aged 6-17 years.
2. TRF reference group: 565 boys and 581 girls, aged 6-17 years.
3. YSR reference group: 347 boys and 383 girls between 11 and 17 years.

For 722 reference children a CBCL questionnaire completed by one of their parents and an YSR completed by the reference child were available. For 1108 reference children a CBCL questionnaire completed by one of their parents and a TRF completed by the teacher of the reference child were available.

The age distributions in the CBCL, TRF and YSR patient samples did not differ significantly from the age distributions in the corresponding reference groups (CBCL: Kolmogorov-Smirnoff Z = 0.59, p = 0.87; TRF: Kolmogorov-Smirnoff Z = 1.04, p = 0.23; YSR: Kolmogorov-Smirnoff Z = 0.54, p = 0.93).

Socioeconomic status (SES) was coded using 3 categories of parental occupation: lower, middle and higher (Netherlands Central Bureau of Statistics, 2001). The SES distribution in the CBCL, TRF and YSR patient samples differed significantly from those in the corresponding CBCL, TRF and YSR reference groups (CBCL: $\chi^2 = 10.34$, df = 2, $p<0.01$; TRF: $\chi^2 = 8.92$, df = 2, $p<0.05$; YSR: $\chi^2 = 8.01$, df = 2, $p<0.05$). This could be attributed mainly to the larger proportions of persons with a low SES in the patient samples (level 1 CBCL, TRF and YSR patient sample respectively: 34.8, 33.8 and 40.0%; reference groups respectively: 23.6, 22.0 and 24.6%). In literature it has been described that the incidence of meningococcal disease was associated with socio-economic deprivation across a rural English region (Stuart et al., 2002).

Assessment procedure

The research protocol was approved by the ethics committee review board before the start of the study. All parents (and their children) were traced, approached uniformly and signed an informed consent before participating in the study. The psychological investigation took place in the department of Child and Adolescent Psychiatry in the ErasmusMC-Sophia Children's Hospital. Parents completed the questionnaires, independently from each other, in the waiting room. When one parent accompanied the child, this parent was asked to deliver the CBCL to his/her partner, if possible. The partner could then complete the questionnaire at home and return it with a prepaid envelope. Parents were also asked to deliver the TRF questionnaire to the teacher, who could return it with a prepaid envelope. Two weeks before the psychological investigation, patients were sent the YSR to complete it at home and bring it with them to the psychological investigation.

Statistical analyses

Deviant range: to distinguish problem children (i.e. scoring in the deviant range) from non-problem children, 90th percentiles of the cumulative frequency distributions of the total problem scores obtained from the reference groups were chosen as the cut-offs, on all three questionnaires. Due to gaps between rank ordered scores, the percentages from the reference groups scoring above the 90th percentile were not exactly 10%.

Age-effects at follow-up: to assess effects of age at follow-up, two age-categories were formed, based on the median split of the patient samples. In the CBCL, TRF and YSR patient samples two age groups were formed for both genders. These categories were respectively 6-11 and 12-17 years (CBCL), 6-10 and 11-17 years (TRF) and 11-13 and 14-17 years (YSR).

Statistical tests: differences in proportions scoring in the deviant range between samples of patients versus reference groups were analyzed by Binomial Testing. Differences in mean scores of samples of patients versus reference groups were assessed with analyses of covariance (AN(C)OVAs). SES was partialled out as covariate since SES-distributions of the samples of patients differed significantly from those of the reference groups. To test differences between different informants (parents, teachers and children) Multivariate Analyses of Covariance (MANCOVAs) were performed on the CBCL, TRF and YSR scales with informant as the within factor. To examine the predictive value of severity of illness and age of the child at time of illness separately on behavioural, emotional and post-traumatic stress problems, linear regression analyses were applied. In these analyses adjustment for follow-up interval (4-16 years) was applied since on several CBCL, YSR and TRF scales the follow-up interval made a significant contribution to the regression model.

Results

Proportions of problem children

Overall, according to parents', teachers' and self-reports, no significant differences were found between the proportions of children scoring in the deviant range in the MSS samples and in the reference groups. The only exception was that according to fathers' reports, the proportion of older MSS boys (12-17 years) scoring in the deviant range was significantly greater (40%) than that of same-aged boys in the reference group (10%). This difference remained significant after Bonferroni correction for five comparisons.

6.7% Of the MSS children were consulting a social worker, a psychiatrist or a psychologist at time of follow-up. This percentage is not significantly different from that of children in the normative reference group who went to a mental health service over the past 12 months (5.9%; Tick et al., in press).

Mean problem scores

To test differences in mean Total Problem scores and mean scale scores, ANCOVAs were computed in a group (patient sample versus reference group) x gender (boys versus girls) x age (CBCL: 6-11 versus 12-17 years; TRF: 6-10 versus 11-17 years; YSR: 11-13 versus 14-17 years) factorial design with SES as a covariate.

Table 1 shows the mean scale scores for the CBCL, TRF and YSR samples of patients and reference groups for the eight scales, the Posttraumatic Stress Problems scale, Internalizing and Externalizing and the Total Problem score, as well as the ANCOVA results. The magnitude of significant ($p<0.05$) group effects (MSS versus reference) is indicated in terms of the percent-

Table 1. Mean problem scores for CBCL, TRF and YSR scales for the MSS samples and reference groups, and percentages of variance accounting for the difference between the MSS and reference group in ANCOVAs

	CBCL mother			CBCL father		
	Mean problem scores		Group*(%)	Mean problem scores		Group*(%)
Scales	MSS (n=86)	Reference (n=1538)		MSS (n=78)	Reference (n=1538)	
Anxious/Depressed	3.1	3.2		2.9	3.2	
Withdrawn/Depressed	1.8	2.1		1.7	2.1	0.7
Somatic Complaints	2.4	1.6	0.9[1]	1.7	1.6	
Social Problems	2.6	2.3		2.6	2.3	
Thought Problems	2.3	2.0		2.1	2.0	
Attention Problems	4.6	3.9		4.2	3.9	
Rule-Breaking Behaviour	1.8	2.0		1.9	2.0	
Aggressive Behaviour	4.9	4.7		4.4	4.7	
Post-traumatic Stress Problems	4.4	4.1		4.2	4.1	
Internalizing	7.3	6.9		6.3	6.9	
Externalizing	6.7	6.7		6.3	6.7	
Total Problems	26.9	25.4		24.5	25.4	

* Percentage of variance accounted for by significant group effect

[1] Significant group effect after Bonferroni correction

Table 1. Continued

	TRF			YSR		
	Mean problem scores		Group*(%)	Mean problem scores		Group*(%)
Scales	MSS (n=61)	Reference (n=1146)		MSS (n=45)	Reference (n=730)	
Anxious/Depressed	3.4	2.9		3.3	4.2	
Withdrawn/Depressed	2.0	2.1		2.2	3.0	0.7
Somatic Complaints	0.5	0.5		3.0	3.0	
Social Problems	2.0	1.7		2.9	3.3	
Thought Problems	0.7	0.5		2.2	3.1	0.4
Attention Problems	10.1	8.5		4.8	5.1	
Rule-Breaking Behaviour	1.6	1.3		4.0	3.9	
Aggressive Behaviour	4.4	3.2		5.5	5.3	
Post-traumatic Stress Problems	3.6	3.1		5.1	6.0	
Internalizing	6.0	5.5		8.4	10.2	
Externalizing	6.0	4.5		9.5	9.2	
Total Problems	25.8	21.4		32.0	35.0	

* Percentage of variance accounted for by significant group effect

[1] Significant group effect after Bonferroni correction

age of variance accounted for. According to Cohen (1988), effects accounting for 1.0 - 5.9% of variance are considered small, 5.9 - 13.8% medium and >13.8% large.

On the CBCL scale Somatic Complaints mothers of MSS children reported significantly more problems than parents of reference children. On the CBCL scale Withdrawn/ Depressed fathers of MSS children reported significantly less problems than parents of reference children. These effects accounted for <1% of the variance and did not meet Cohen's criteria (Cohen, 1988) for small effects. The group effect on Somatic Complaints for mothers remained significant after Bonferroni correction for 12 comparisons, the group effect on Withdrawn/Depressed however did not.

One significant group x gender interaction effect ($p=0.01$) was found on CBCL Somatic Complaints, with fathers as informants. This effect showed that for MSS boys more somatic complaints were reported than for MSS girls, whereas in the reference group for girls more somatic complaints were reported than for boys. This difference, however, did not remain significant after Bonferroni correction for 12 comparisons.

No further main group effects, nor group x gender or group x age interaction effects were found on the CBCL (mother and father) or TRF scales.

On the YSR a significant group effect on Withdrawn/Depressed and on Thought Problems indicated that MSS children reported these problems significantly less often than reference children. Again, according to Cohen (1988) these effects were <1% and did not meet the criteria for small effects. After Bonferroni correction these effects did not remain significant.

For YSR Total Problems, a significant group x gender interaction effect was found ($p=0.04$). This effect showed that in the MSS group boys showed more problems than girls, whereas in the reference group girls reported more problems than boys. For YSR Somatic Complaints, a significant group x age interaction effect was found. This effect showed that older MSS children (14-17 years) reported more somatic complaints than younger MSS children (11-13 years), while in the reference group younger children scored more somatic complaints than older children. These interaction effects did not remain significant after Bonferroni correction for 12 comparisons.

Severity of illness and age at time of illness

Severity of illness did not appear to be a significant predictor for long-term total problem scores and scale scores, neither when parents were the informants, nor when teachers, nor when children themselves were the informants.

Age at time of illness appeared to be a significant predictor of long-term post-traumatic stress, social, and total problems, when mothers were informants (post-traumatic stress problems: $\beta= -0.36$, $p<0.05$; social problems: $\beta= -0.32$, $p<0.05$; total problems: $\beta= -1.79$, $p<0.05$). When fathers were informants, age at time of illness was a significant predictor of long-term post-traumatic stress, anxious/depressed, attention and total problems (post-traumatic stress problems: $\beta= -0.43$, $p<0.05$; anxious/depressed: $\beta= -0.33$, $p<0.05$; attention problems: $\beta= -0.42$, $p<0.05$; total problems: $\beta= -2.23$, $p<0.05$). Younger age was significantly associated with higher scores on these CBCL problem scales. This indicated that the younger the child at time of illness, the more of these problems on the long term.

When teachers or children themselves were informants, age at time of illness did not appear to be a significant predictor for long-term total problem scores and scale scores.

Different informants

To test effects of different informants (parents versus children), MANCOVAs were performed on the scores of 11-17-year-old MSS patients and reference children with both a CBCL and YSR completed. Significant informant x group interaction effects were found on Thought Problems ($p<0.05$), indicating larger differences between the scores of children and mothers in the reference group compared to the MSS sample. In both samples children reported more problems than their parents did. On Thought Problems a significant informant x group effect was found when fathers completed the CBCLs ($p< 0.01$). This effect indicated that on this scale more problems were reported by MSS fathers than by the MSS children themselves, whereas in the reference group children themselves reported more problems than their parents did about them. Another significant informant x group effect was found on Social Problems ($p<0.05$) indicating that MSS fathers reported more problems on this scale than MSS children themselves whereas in the reference group the reverse pattern was found.

To test effects of parents versus teachers, MANCOVAs were performed on the scores of 6-17-year-old MSS patients and the reference group with both a CBCL and TRF completed. Two significant informant x group interaction effects were found on the scales Thought Problems ($p<0.05$) and Somatic Complaints ($p<0.05$), when mothers filled in the CBCL. Both effects indicated larger differences between the scores of mothers and scores of teachers in the MSS sample compared to the reference group. In both samples mothers reported more thought problems and more somatic complaints than teachers.

When fathers filled in the CBCL, no significant informant x group interaction effects were found.

Discussion

Behavioural, emotional and post-traumatic stress problems in patients versus reference children

Overall, according to mothers', fathers', teachers' and patients' reports, the proportions of MSS children and adolescents scoring in the deviant, psychopathological range were comparable to those in the reference groups. Only one significant difference was found; according to fathers significantly more (40%, n=20) older MSS-boys (12-17 years) showed problem behaviour falling in the deviant range in comparison with same-aged reference boys (10%).

As to the level of emotional and behavioural problems: mothers reported more somatic complaints for their children in comparison to the reference group. This could be due to frequently reported complaints of headache, stomach-ache and skin problems.

Fathers of patients reported less symptoms of withdrawn/depressed behaviour for their children compared to the reference group. MSS-children and adolescents themselves also reported less symptoms of withdrawn/depressed behaviour and less thought problems in comparison to reference peers. These trends in MSS children's reports and fathers' reports may reflect resilience in youth. It can be speculated, that after a life-threatening disease as MSS, youngsters may me more inclined to appreciate and enjoy life more. This might result in less withdrawal or depressive complaints.

Our results are in contrast with those of Fellick et al. (2001). They found worse results, compared to controls, on behavioural measures in survivors of meningococcal infection, 8 years after illness. However, their patient sample was heterogeneous, consisting of patients with meningococcal meningitis, meningococcal septicaemia and mixed disease. Furthermore Fellick et al. used a different questionnaire. Koomen (2003) found that one third of the children who survived bacterial meningitis without severe sequelae, showed behavioural and/ or academic limitations 4-10 years after illness. However, bacterial meningitis is a disease with a different pathophysiology than MSS and therefore different outcomes were to be expected. Our results as to post-traumatic stress problems are in line with those of Rees et al. (2004). They found that the prevalence and intensity of PTSD symptoms seem to diminish over time in children who had been admitted to a PICU. However, in their study children with MSS were not included.

An explanation for our findings is that although at time of illness the emotional impact is enormous, children have learned to cope with the impact of illness and show resilience. In semi-structured interviews parents reported that for most of the children daily life goes on. Overall, parents expressed their belief that their children did not have more problems than reference children. Other remarks of parents may also indicate resilience. When asked whether or not the child at present did experience disadvantages due to MSS, parents often reported that there were no such disadvantages. Instead parents often stated the disease had made their child stronger. In this context it is relevant to consider that the percentage of MSS children visiting a mental health care service at time of follow-up was similar to that in the normative reference group (Tick et al., in press).

Resilience in children and adolescents was also found in other studies into psychosocial consequences of mass violence, terrorism and disasters (Caffo & Belaise, 2003; Williams, 2007). Moreover, resilience has been connected to socio-economic status (SES)(Kim-Cohen et al., 2004; Sameroff & Rosenblum, 2006). In some studies, it has been found that children may successfully adapt to their socio-economic disadvantageous situation and become resilient (Kim-Cohen et al., 2004). If such children do survive a life-threatening illness, this might make then less vulnerable to be harmed. It might be possible that our patients have been toughened by living in a more disadvantageous socio-economic situation and having survived a life-threatening illness. However, low socio-economic status is also a well-known risk factor for negative behavioural and cognitive outcome (Sameroff & Rosenblum, 2006).

The proportions of parents with a low SES in our samples of patients were larger than those in the normative reference groups. Therefore, we adjusted for SES in this study.

Another explanation for our results may be that parents might have given more attention and/or emotional warmth to their child, after almost having lost the child to a severe illness. A nurturant involvement of a primary caregiver is a factor that promotes resilience in high-risk low-income samples (Wyman et al., 1991).

Finally, a possible explanation for our findings may be that parents aren't bothered too much by possible behavioural and emotional problems of their child. During the interviews parents commented they counted themselves lucky since their child was still alive. This might have affected the way parents perceived their child and the way they completed the questionnaires.

Effect of gender and age at follow-up on the level of behavioural, emotional and post-traumatic stress problems

Overall, the results indicate that MSS boys experience the most problems and that they show more problems at an older age.

Relation between severity of illness and age at time of illness and behavioural, emotional and post-traumatic stress problems

Severity of illness was not a significant predictor of behavioural, emotional or post-traumatic stress outcomes at follow-up. Our results as to age at time of illness indicated that if children got sick at a younger age, they were at higher risk for behavioural, emotional and post-traumatic stress problems, both according to their mothers and fathers. A possible explanation is that there is no rooming in at the PICU and especially for preschoolers being separated from their parents is more traumatic than for older children. Stuber and Shemesh (2006) describe that younger children are more likely than older children to find separation from friends and family to be a major traumatic event.

Discrepancies between different informants

The difference between mothers' and children's reports regarding thought problems was smaller in the MSS sample than in the reference group. In both the MSS sample and reference group, children themselves reported more thought problems than their mothers did about them. A possible explanation might be that MSS mothers and MSS children have become closer to each other and therefore MSS mothers may have perceived thought problems of their child more adequately. Fathers of MSS children reported more thought and social problems compared to the MSS children themselves, whereas in the reference group parents reported less such problems about their children compared to the children themselves.

The difference between scores of mothers and teachers as to thought and somatic problems was larger in the MSS sample than in the reference group. In both the MSS and reference samples mothers reported more such problems than teachers did. Due to the MSS, mothers of patients may have become more alert to problems of their child and therefore are more prone to report these compared to teachers. Therefore this trend may be stronger in the patient sample compared to the reference sample.

Strengths and limitations of the present study

A unique feature of this study is the use of a homogeneous patient sample, consisting of only MSS patients. The follow-up interval was at least 4 years (4-16 years) after the disease. In contrast to other studies four different informants were used (mothers, fathers, teachers and children) and standardized assessment procedures were used. Furthermore the response rates were high.

This study has been done in one centre, and it is unknown to what extend idiosyncrasies of one centre may have influenced our results. Statistical analyses showed differences in baseline characteristics (age, sex and severity of illness) between responders and non-responders. Data from the patient sample was gathered immediately after the period in which the normative data was gathered, so the data gathering periods do not overlap. It is unknown to what extend this last difference and the fact that responders and non-responders differed as to baseline characteristics may have influenced our findings. In the PICU it is not feasible to find another critical illness with the same amounts of patients and age distribution, so we chose large representative normative samples to compare our data with.

Implications

Overall, long-term behavioural, emotional and post-traumatic stress outcomes of MSS children were comparable to those of normative reference groups. We need to remain alert however, for individual children at risk of behavioural and/or emotional and/or post-traumatic stress problems.

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4

Self-esteem in children and adolescents after septic shock caused by *Neisseria meningitidis:* scars do matter

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Abstract

Aims

To investigate self-esteem, and its relation with scars, amputations and orthopedic sequelae in children and adolescents long-term after septic shock caused by *Neisseria meningitidis* (MSS).

Methods

The Dutch versions of the Self-Perception Profile for Children (SPP-C; 8-11 years) and the Self-Perception Profile for Adolescents (SPP-A; 12-17 years) were used to assess self-esteem. The Patient and Scar Assessment Scale (PSAS) was used to evaluate scar severity.

Results

MSS boys aged 8-11 years obtained higher, more favorable scores on self-esteem while same-aged MSS girls reported comparable levels of self-esteem compared to respectively same-aged reference boys and girls. MSS boys and girls aged 12-17 years obtained unfavorable scores on self-esteem compared to respectively same-aged reference boys and girls. Overall, gender did not have an effect on self-esteem. Severity of illness, age at time of illness and age at time of follow-up were not significant predictors of self- esteem. MSS adolescents with scars reported lower global self-worth than MSS adolescents without scars. The worse MSS children evaluated their scars, the worse their outcomes on social acceptance. The worse MSS adolescents evaluated their scars, the worse their outcomes on close friendship, but the better their outcomes on social acceptance and behavioural conduct.

Conclusion

In this cross-sectional study favorable outcomes for self-esteem were found in MSS children, whereas MSS adolescents reported lower self-esteem compared to reference adolescents. Adolescents with scars reported lower global self-worth than MSS adolescents without scars.

Introduction

Septic shock with petechial and/or purpuric rash is a severe syndrome predominantly caused by *Neisseria meningitidis* and characterized by a very sudden onset and a fulminant course. Previously healthy children become suddenly very ill and are admitted to a Pediatric Intensive Care Unit (PICU). Children with this critical illness, also known as Meningococcal Septic Shock (MSS), are one of the most severely ill and unstable groups of children admitted to a PICU. A previously healthy child may die within 24 hours. Despite advances in knowledge about pathophysiology and treatment, there is still a high morbidity and mortality (19%) (Baines & Hart, 2003).

MSS may result in somatic sequelae like scars, amputation(s) of digit(s) or limb(s) as a result of skin necrosis, and limited motor functioning because of these amputations and orthopedic sequelae (Erickson & Wals, 1998; Erickson et al., 2001; Wheeler et al., 2003; Belthur et al., 2005; Bache & Torode, 2006). We hypothesize that such sequelae can have a negative influence on the self-esteem of child- and adolescent-survivors of MSS. Self-esteem is the evaluation of the self concept, which is defined as the total of ideas and notions that a person has about herself of himself (Harter, 1988).

Self-esteem is important for the development and general functioning of youths and is related to academic achievement, social functioning and psychopathology (Bos et al., 2006). There is much debate about how to define self-esteem (global versus a domain-specific construct), and consequently how it should be assessed. Recent research gives insight into how self-esteem varies over different ages and gender, and how it effects health (Birndorf et al., 2005). Generally the level of global self-esteem is relatively high during childhood and it drops dramatically when children enter adolescence (Robins et al., 2002). Several studies (Kling et al., 1999; a meta-analysis; Birndorf et al., 2005) showed that boys report higher self-esteem than girls. Furthermore, high self-esteem has been shown to be associated with better mental health outcomes (better ability to cope, lower incidence of depression), but did not appear to be a significant predictor of physical disease (Birndorf et al., 2005). Dubois and Hirsch (2000) distinguished among multiple aspects of self-esteem and developed a general conceptual framework of self-esteem in early adolescence. In this framework self-esteem is multidimensional in structure, influenced by a complex, interdependent group of individual factors (such as cognitive and affective developmental status) and contextual factors (such as peers, family and school), with bidirectional linkages to adjustment outcomes.

Several studies have reported favourable outcomes regarding self-esteem in children and adolescents with asthma, congenital heart disease (ConHD) and epileptic surgery, whereas in children after traumatic brain injury or liver transplantation lower self-esteem was reported (Wray & Sensky, 1998; Boeckaerts & Röder, 1999; Van Empelen et al., 2005; Andrews et al., 1998; Törnqvist et al., 1999). Lower and higher outcomes of self-esteem were found in burn-patients 1-17 years post-burn (LeDoux et al., 1996; Robert et al., 1999). In almost all studies cited the Harter Self-Perception Profiles for children (SPP-C) (Harter, 1985) and/ or for adolescents (SPP-A) (Harter, 1988) were used (except study Wray & Sensky, 1998 and Andrews et al., 1998).

Self-esteem has never been investigated in children and adolescents who survived MSS before. Therefore the present study was started to investigate the long-term outcome on self-esteem in a homogeneous cohort of children and adolescents who survived MSS between 1988 and 2001. The aims of the present study were:

1. To compare the levels of self-esteem of MSS children and adolescents with those of reference groups.
2. To examine the predictive value of severity of illness, age at time of illness and age at time of follow-up on self-esteem and to identify the role of gender on self-esteem.
3. To identify the role of the presence of scars and of amputations and orthopedic sequelae on self-esteem and to investigate the relationship between the evaluation of scars and self-esteem.

Methods

Instruments

Self-Perception Profile for Children (SPP-C) and Self-Perception Profile for Adolescents (SPP-A)

Self-esteem was measured with the Dutch versions (Veerman et al., 1997; Treffers et al., 2002) of Harter's Self-Perception Profile for Children (SPP-C) (for ages 8-11) (Harter, 1985) and Harter's Self-Perception Profile for Adolescents (SPP-A) (for ages 12-17) (Harter, 1988). The questionnaires consist of 36 (SPP-C) and 40 (SPP-A) items, which are distributed over five domain-specific subscales and one global self-worth subscale (see Table 2 and 3). High scores are favorable, low scores are unfavorable. The internal consistency of the Dutch SPP-C subscales varies from 0.70 to 0.82 (except for the behavioral conduct subscale: 0.68) (Veerman et al., 1997). The test-retest reliability varies from 0.74 to 0.86, (except for Social Acceptance: 0.68). The internal consistency of the Dutch SPP-A subscales varies from 0.73 to 0.88 (except for scholastic competence: 0.66) (Treffers et al., 2002). The rest-retest reliability varies from 0.72 to 0.87 (except for Social Acceptance: 0.67).

PRISM-score

The Paediatric Risk of Mortality (PRISM) score, a validated score to express the severity of illness, was used as index of severity of illness (Pollack et al., 1988). The score is calculated on the basis of the most abnormal values for physiological variables during the first 24 hours of admission to an Intensive Care Unit.

PSAS-score

The Patient Scar Assessment Scale (PSAS) is part of the Patient and Observer Scar Assessment Scale-scoring system (POSAS) and is one of the very few validated scoring systems to assess the severity of skin scarring (Draaijers et al., 2004). The PSAS is the patient-part and is completed by the child or adolescent with the scar together with their parent(s). The child or adolescent scores the 6 scar-characteristics: scar colour, pliability, thickness, relief, itching and pain on a 10-step score, whereby the score 10 reflects the worst imaginable scar or sensation (score range: 6-60). The internal consistency of the patient scale was acceptable (= 0.76) (Draaijers et al., 2004).

Description of the sample

Inclusion and exclusion criteria

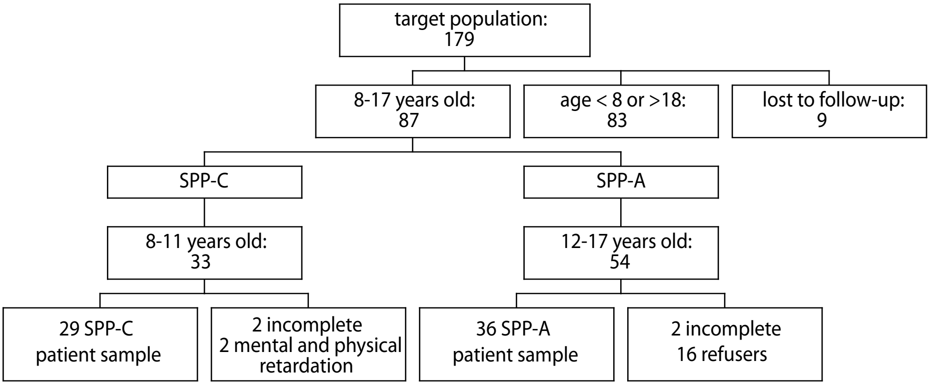
During the follow-up, which took place in 2005-2006, consecutive surviving patients with a clinical picture of meningococcal septic shock, defined as septic shock with petechiae/purpura, requiring intensive care treatment at the PICU of ErasmusMC-Sophia Children's Hospital at least four years ago (between 1 August 1988 and 1 June 2001) were eligible. This will be called MSS from now on. In 83% of the patients *Neisseria meningitidis* was cultured. Parents and patients who were not Dutch speaking were excluded.

In the present study 8-17-year-old (ex-) patients were included since this age-range was covered by the questionnaires used.

Patient sample

The target population consisted of 179 consecutive surviving patients (see Figure 1). At follow-up 9 patients were lost (7 moved abroad, 1 deceased and 1 untraceable). Of the remaining 170 patients, 87 patients in the age-range of 8-17-year old were eligible (since this

Figure 1. Inclusion of patients



was the age-range covered by the questionnaires). Sixteen patients refused to participate on practical or emotional grounds (for example didn't want absence from school or didn't want a renewed confrontation with the hospital). The final sample consisted of 29 patients (mean age: 9.4 years) who filled in the SPP-C (8-11 years) and 36 patients (mean age: 14.4 years) who filled in the SPP-A (12-17 years). The response rate (corrected for deceased persons and persons lost to follow-up) was 88% (29/33) for the SPP-C and 67% (36/54) for the SPP-A.

Socio-economic status (SES) was scored on a 3-point scale of parental occupation (see Table 1). SES-level 1 corresponds with elementary, 'lower' occupations, SES-level 2 with 'middle' occupations and SES-level 3 with 'higher' and scientific occupations (Netherlands Central Bureau of Statistics, 2001). When both parents had a paid job, the highest SES-level of occupation was used.

Table 1. Characteristics of patient sample

	SPP-C N=29 (100%)	**SPP-A N=36 (100%)**
Gender distribution		
Boys	13 (45%)	20 (56%)
Girls	16 (55%)	16 (44%)
Socio-economic status*		
SES-level 1	10 (34%)	14 (39%)
SES-level 2	13 (45%)	16 (44%)
SES-level 3	6 (21%)	6 (21%)
Presence of scars	15 (52%)	18 (50%)
Positions of scars:		
face	3 (20%)	6 (33%)
trunk	1 (6%)	4 (22%)
arms	6 (40%)	10 (56%)
legs	12 (80%)	16 (89%)
unknown	3 (20%)	0 (0%)
Presence of amputations	2 (7%)	3 (08%)
Amputations of:		
one toe	1 (50%)	0 (0%)
four toes	1 (50%)	0 (0%)
one finger	0 (0%)	1 (33%)
one leg (below-knee)	0 (0%)	1 (33%)
one arm (below-elbow) and two legs (one below knee and one above knee)	0 (0%)	1 (33%)
Presence of orthopedic sequelae	2 (7%)	0 (0%)
Orthopedic sequelae:		
lower limb-length discrepancy (3.5 cm)	1 (50%)	0 (0%)
varus deformity of the right ankle	1 (50%)	0 (0%)

*Abbreviations: SES: socio-economic status

Reference groups

The reference groups for the SPP-C and the SPP-A consisted of representative normative samples of healthy children and adolescents used to standardize these questionnaires (Veerman et al., 1997; Treffers et al., 2002).

Assessment procedure

The research protocol was approved by the ethics committee review board. All parents and their children were traced, approached uniformly and signed an informed consent. During the psychological investigation at the ErasmusMC-Sophia Children's Hospital, participants completed the questionnaires after being instructed by the psychologist. A physical examination was performed by a pediatric intensivist (CB), with special focus on scars, amputations, angular deformity and limb-length discrepancy, related to MSS.

Statistical analyses

All analyses were performed with two-sided tests; $p < 0.05$ was considered significant. One-sample t-tests were used to test differences in group means between the patient sample and reference groups. Only results that are significant after Bonferroni correction are presented. Socio-economic status showed a significant main effect in ANOVAs on five of six scales of the SPP-C, indicating lower self-esteem in lower SES classes. It was decided to apply SES as covariate in analyses on the SPP-C. For the SPP-A there was no significant main effect of SES in ANOVAs on any of the scales. It was decided to not apply SES as covariate in analyses of the SPP-A.

To identify the role of gender within the patient sample AN(C)OVA's, were performed on all SPP-C and SPP-A scales.

To examine the predictive value of severity of illness, age of the child at time of admission, and age at time of follow-up separately on self-esteem, linear regression analyses were applied. Follow-up interval (4-16 years) did not deliver a significant contribution to the regression analyses and there for was not adjusted for.

To identify the role of the presence of scars (scars versus no scars) within the patient sample ANOVAs were performed on all scales of the SPP-C and SPP-A. The relationship between the severity of scars (patient-part POSAS) and self-esteem was investigated by calculating Pearson correlations.

To identify the role of the presence of amputations and orthopedic sequelae, a non-parametric exact test (Mann-Whitney U-test) was used to test differences in group means between the patient sample with amputations and orthopedic sequelae and the patient sample without amputations and orthopedic sequelae on respectively the SPP-C and SPP-A.

Results

Comparison of levels of self-esteem of MSS children and adolescents versus reference groups

MSS boys aged 8-11 years obtained a more favourable score on Social Acceptance compared to same-aged reference boys (Table 2). No further differences were found on any of the SPP-C-scales between mean scale scores of MSS boys versus those of same-aged reference boys, neither between the mean scale scores of MSS girls in the age range 8-11 years versus those of same-aged reference girls.

MSS boys aged 12-17 years obtained significant lower mean scores, indicating poorer functioning, compared to same-aged reference boys on 6 of 7 SPP-A scales: scholastic competence, social acceptance, athletic competence, physical appearance, close friendship and global self-worth.

MSS girls aged 12-17 years reported poorer functioning compared to reference girls on 3 of 7 SPP-A scales: social acceptance, close friendship and global self-worth.

Effect of gender within the patient sample

Although the first analysis indicated a gender effect on one scale (adolescent MSS boys obtained more unfavorable scores on behavioral conduct than adolescent MSS girls), after Bonferroni correction no main effects of gender were found within the sample of MSS children respectively MSS adolescents, on any of the SPP-C respectively SPP-A scales.

Relationship between severity of illness, age at time of illness and age at time of follow-up, and self-esteem

Severity of illness, age at time of illness and age at time of follow-up did not appear to be significant predictors for long-term SPP-C and SPP-A scores in MSS children and adolescents.

Relationship between scars, amputations and orthopedic sequelae and self-esteem

- *Relationship between presence of skin scarring and self-esteem*

Table 1 indicates the incidence of skin scarring due to necrotic purpura at the time of MSS. ANOVAs revealed no differences on any of the SPP-C scales between the mean scale scores of MSS children with scars versus MSS children without scars.

Table 2. Mean scale scores on the Self-Perception Profile for Children of the MSS children and the reference groups

	MSS children		**Reference**	
	Girls (n=16)	**Boys (n=13)**	**Girls (n=181)**	**Boys (n=180)**
Scales	**Mean**	**Mean**	**Mean**	**Mean**
Scholastic Competence	16.0	16.5	16.3	17.4
Social Acceptance	17.7	19.9[1]	17.5	17.8
Athletic Competence	17.4	18.0	17.6	18.7
Physical Appearance	18.6	21.2	18.9	20.1
Behavioral Conduct	18.4	16.9	18.0	17.0
Global Self-Worth	20.3	19.7	19.4	20.0

A low scale score is indicative of unfavorable self-esteem.

[1] Significant ($p<0.05$) difference between MSS children versus same-sex reference children.

Table 3. Mean scale scores on the Self-Perception Profile for Adolescents of the MSS adolescents and the reference groups

	MSS adolescents		Reference	
	Girls n=16	Boys n=20	Girls n=785	Boys n=601
Scales	**Mean**	**Mean**	**Mean**	**Mean**
Scholastic Competence	13.4	13.4[1]	13.1	14.5
Social Acceptance	13.2[1]	13.1[1]	15.4	15.3
Athletic Competence	12.6	12.3[1]	12.4	14.8
Physical Appearance	12.3	12.7[1]	12.7	14.7
Behavioral Conduct	14.3	13.3	14.8	13.8
Close Friendship	12.3[1]	12.1[1]	17.7	16.6
Global Self-Worth	11.6[1]	12.0[1]	14.9	16.0

A low scale score is indicative of unfavorable self-esteem.

[1] Significant ($p<0.05$) difference between MSS adolescents versus same-sex reference adolescents.

MSS adolescents with scars reported a significantly lower global self-worth compared to adolescents without scars. No further effects were found of the presence of scars on any other SPP-A scale.

- *Evaluation of scars and self-esteem*

For MSS children with scars (n=17), a significant negative correlation was found between their scar evaluations and scores on the SPP-C scale social acceptance. The more unfavorable the children evaluated their scar, the lower their score on social acceptance.

For MSS adolescents with scars (n=18) a significant negative correlation was found between the PSAS score and close friendship, indicating the more unfavorable the evaluations of the scar, the more unfavorable the scores on close friendship. A significant positive correlation was found between the evaluations of the scars and respectively scores on social acceptance and behavioral conduct. These correlations indicated that worse evaluations of the scars were related to more favorable scores on those scales.

No further significant correlations were found between the PSAS and SPP-C respectively SPP-A scores.

- *Presence of amputations and orthopedic sequelae, and self-esteem*

Table 1 indicates the incidence of amputations and orthopedic sequelae. When MSS children with orthopedic sequelae or amputations (n=4) were compared to MSS children without orthopedic sequelae or amputations, no significant differences in self-esteem were found, nor when MSS adolescents with amputations (n=2) were compared with MSS adolescents without amputations.

Discussion

Comparison of levels of self-esteem with reference groups

MSS adolescents showed lower self-esteem scores compared to reference adolescents while MSS children showed similar self-esteem scores compared to reference children.

MSS boys in the age range 8-11 years old reported to feel more socially accepted than same-aged reference boys. For 8-11 years old MSS girls no differences were found on any of the self-esteem scales in comparison with reference girls. A meta-analysis of Kling et al. (1999) confirms that in the general population boys show more favorable outcomes on self-esteem than girls. The same was found in the reference group; on nearly all scales reference boys score higher than reference girls (Veerman et al., 1997). Gender differences as to self-esteem may be due to gender roles. Many qualities associated with the male role are consistent with high self-esteem, and self-confidence is stereotyped as a masculine characteristic (Kling et al., 1999). Furthermore, our positive findings as to the boys are in line with a study of boys (aged 8-12 years) 2 years after epileptic surgery (Van Empelen et al., 2005). In this study boys were postoperatively socially more competent and they had greater self-worth compared to their pre-operative scores. Results are difficult to compare since MSS children were healthy prior to disease, whereas epileptic children may have had lower self-esteem pre-operatively because they avoided social activities due to fear of seizures. Concerning girls, our results are in line with children with congenital heart disease (aged 5-15 years) 1 year after surgery and children with asthma and diabetes (age range 7-16 years) (Wray & Sensky, 1998; Boeckaerts & Röder, 1999).

Overall, in this study outcomes on self-esteem for MSS children are more favorable than for MSS adolescents. This is in line with trends in the general population: a dramatic decrease in self-esteem during the transition from childhood to adolescence is often reported (Major et al., 1999; Robins et al., 2002). Adolescence is a stressful developmental stage with marked biological, social, cognitive, psychological and academic changes and the transition from primary school to secondary school. Boys and girls become sexually mature and are searching for a mate, while as to cognitive development they gain the capacity of formative thinking. Adolescents are focused more on peers than on family, and therefore are vulnerable to feelings of insecurity and vulnerability. Having experienced a life-threatening illness as MSS may increase feelings of vulnerability and on the long term negatively influence self-esteem of adolescents in this already complex phase of their lives. This might explain why adolescents reported lower scores on self-esteem compared to reference adolescents.

Moreover, our findings are comparable with those of 14-18 year old boys and girls who underwent liver transplantation 2-12 years ago. Boys found themselves less competent on nearly all self-esteem-scales (Törnqvist et al., 1999) and girls found themselves less competent in 3 of 7 competence-scales. The reason that MSS adolescents feel less competent might be the awareness of the previous life-threatening disease that makes them feel vulnerable. Adolescents may be more preoccupied with their bodies and due to the capacity of formative thinking be more aware of the life-threatening aspect of the critical illness and its possible consequences than children are.

The effect of gender on self-esteem and the relationship between severity of illness, age at time of illness and age at time of follow-up on self-esteem

Within the sample of MSS survivors no effects of gender on self-esteem were found, nor for children nor for adolescents. This is in contrast with trends in the general population showing a higher self-esteem in boys than in girls (Veerman et al., 1997; Treffers et al., 2002; Birndorf et al., 2005). According to Bos et al. (2006) however, research on gender differences in childhood self-esteem has yielded inconsistent results. Our lack of gender effects may be explained by the Sociometer Theory (Leary et al., 2000). According to this theory children easily adopt the views that important others, such as their parents, have about them (Leary et al., 2002). Parents whose child has had a life-threatening illness might be more approving, responsive and nurturing towards the child, which enhances self-esteem. Such a nurturing parental attitude might give an extra boost to MSS children with a lower self-esteem and thus might decrease the possible discrepancies between boys and girls.

Severity of illness, age at time of illness and age at time of follow-up did not appear to be significant predictors of self- esteem. These findings are in line of those for children after traumatic brain injury (Andrews et al., 1998).

Relationship between scars, amputations and orthopedic sequelae and self-esteem

- *Presence and evaluation of scars*

Overall, MSS children with and without scars showed comparable outcomes on all self-esteem domains. MSS adolescents with scars, however, reported a lower global self-worth than adolescents without scars.

The worse children evaluated their scars, the worse their scores on social acceptance. Worse evaluations of scars by adolescents, however, were related to worse outcomes on close friendships, but also to better outcomes on social acceptance and behavioural conduct.

Our results might be compared with those of children after burns. In a study of children (10-13 years) and adolescents (14-17 years), 1 to 5 years post burn higher self-esteem in 2 domains was found (LeDoux et al., 1996). Both groups reported a higher competence as to social acceptance, while the adolescents described themselves as having greater romantic appeal and the children tended towards a more favourable global self-worth.

In a study of 14 adolescents (13-20 years old) at least 2 years post-burn injury lower scores on athletic competence and physical appearance and higher scores on social acceptance and job competence were found (Robert et al., 1999). The different findings between adolescents with burns compared with our investigated group adolescents with MSS can be explained by the fact that in the previous mentioned studies adolescents with scars were compared with normative adolescents whereas in our study MSS adolescent with scars were compared to MSS adolescents without scars. Furthermore the study samples in the "burn studies" were different from ours (smaller sample size, different age range and different follow-up interval).

Physical appearance is closely linked with global self-esteem (Harter, 1993). Research showed body image to be the strongest unique predictor of overall feelings of self-worth (Harter, 1993; Dubois et al., 1996; Dubois et al., 2000). Interestingly, in our study MSS adolescents with and without scars didn't show differences on the physical appearance scale. This is in line with findings in the general population where youths rated physical appearance, with the exception of sports/athletics, as less important for their self-esteem (Dubois et al., 2000). Dubois et al. (2000) state that "many adolescents are not fully cognizant of the extent to which body image constitutes a significant influence on their feelings about themselves". A possible explanation for the lower global self worth of MSS-adolescents might be that they perceive the scars as symbolic constant reminders of having experienced a life-threatening illness, which might result in feelings of vulnerability. Our findings are in line with those of studies concerning chronic disorders, which also failed to identify visibility of the disorder as a risk factor for impaired self-esteem (Ireys et al., 1994; Aasland & Diseth, 1999). Furthermore we found for MSS adolescents that worse evaluation of scars was related to worse outcome on intimate relations (close friendship) and to better outcomes on social acceptance and behavioural conduct. Fear of rejection and elevated feelings of vulnerability might be the reason that MSS adolescents have less self-esteem in the particular "intimacy" domain. Adolescents are in a special developmental stage; they are becoming sexually mature and are searching for a mate. The present favourable outcomes on social acceptance and behaviour are on a less intimate level and may be a result of strategies adolescents may use in the face of failure in a particular domain (Bos et al., 2006). Downward social comparison (for example comparing oneself with others with more severe visible anomalies) may help adolescents to protect, maintain or enhance their self-esteem levels (Bos et al., 2006). Adolescents may reduce the importance of a domain in which they fail to achieve success (Bos et al., 2006). Thus MSS adolescents with worse scarring might devaluate physical appearance as less important, and might perceive social acceptance and behavioral conduct as more important. The latter has been described by Crocker & Park (2003) and by Harter (1999), who called it the discounting-hypothesis. Furthermore Dubois et al. (2000) describe that personal internal standards or aspirations are important aspects of self-esteem. These standards or aspirations might change when having survived a life-threatening disease.

In our study the worse MSS children evaluated their scars, the worse their scores on social acceptance. A possible explanation for this might be that in childhood scars may evoke anxious reactions of peers who may be afraid of contagion. Because children have limited cognitive capacities, they may not fully understand the "dangerousness" of scars and consequently MSS children with scars might be avoided.

Peers of MSS adolescents however are capable of more abstract reasoning and may put the scars into perspective more easily than children do, which may result in better social acceptance. MSS adolescents may appreciate and value having social contacts (despite their scars) more than "than normal" after having survived a life threatening disease. Furthermore, for MSS adolescents having scars, as symbolic reminders of survival ("battle scars") may contribute in their search for an own identity. They may derive a feeling of being somewhat special because of their "battle scars", which may give them feeling of competence in social contacts.

- *Presence of amputations and orthopedic sequelae*

Since the number of patients with orthopedic sequelae or amputations was very small, it is difficult to draw reliable conclusions from these results.

Strengths and limitations of the present study

Self-esteem has not been investigated in children and adolescents who survived MSS before, neither on the short-term, nor on the long-term. Standardized assessment procedures were used and the response rate was high.

The concept of self-esteem is difficult to capture. There is still much debate on how to define self-esteem and how to assess it (Dusek, 2000). Many research has linked self-esteem with other mental or physical constructs, uni- or bidirectional, but the picture is not yet clear. The present long-term outcomes on self-esteem indicate associative, not causal relationships.

This cross-sectional study has been done in one centre, and question marks can be set at generalizability to other centres. Although the response rate was high, small numbers of patients in sub-groups were investigated. Therefore caution should be made in drawing firm conclusions. Finally, this was not a longitudinal study so it is unclear to what extent self-esteem problems might persist when the adolescents get older.

Implications

Overall, in this cross-sectional study the long-term outcome on self-esteem was favorable in MSS children, but unfavorable in MSS adolescents.

We need to be alert for individual MSS adolescents in the age range 12-17 years who are at risk for having low self-esteem. Considering our results, we intend to start a standardized multidisciplinary follow-up clinic and to develop guidelines for preventive therapeutic interventions, especially aimed at adolescent survivors of MSS.

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Survivors of septic shock caused by *Neisseria meningitidis* in childhood: psychosocial outcomes in adulthood

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Abstract

Aims

To gain insight into long-term psychosocial outcomes in adults who survived septic shock, caused by *Neisseria meningitidis* (MSS) during childhood, we examined the biographical characteristics, illness-related physical or social consequences, intellectual functioning and behavioural and emotional problems.

Methods

Included were 16-31 year-old patients who survived MSS and were admitted to the Paediatric Intensive Care Unit (PICU) between 1988 and 2001. A semi-structured interview was used to assess biographical characteristics and illness-related physical or social consequences. A standardized intelligence test, the Groninger Intelligence Test 2 (GIT2), was used to assess intellectual functioning. The Adult Self-Report (ASR) was used to assess behavioural and emotional problems.

Results

In total 58 MSS patients participated in this study (response rate: 70%, median follow-up interval: 13 years, range 4-16 years). Overall, MSS patients did not differ from reference groups as to biographical characteristics. The majority of MSS patients did not report illness-related physical or social consequences. Overall, intellectual functioning and levels of behavioural and emotional problems of MSS patients were comparable to those of the reference group.

Conclusion

Despite the large physical and psychological impact of MSS on the short-term, long-term psychosocial outcomes in adults were favourable as to biographical characteristics, illness-related physical or social consequences, behavioural and emotional problems and intellectual functioning.

Introduction

Meningococcal disease (MD) encompasses 3 different entities: meningitis, sepsis and septic shock. The most severe entity of MD is septic shock with petechial and/or purpuric rash which is a life-threatening clinical syndrome caused by *Neisseria meningitidis*. It occurs predominantly in children and adolescents, is characterised by an abrupt, unexpected onset, a fulminant course and necessitates immediate admission to a Paediatric Intensive Care Unit (PICU). In a matter of hours a previously healthy child may die. Children with this syndrome, also called Meningococcal Septic Shock (MSS), are one of the most severely ill and unstable groups of children admitted to a PICU. Despite advances in knowledge about pathophysiology and treatment, morbidity and mortality remain high (19% Baines & Hart, 2003; 15.7% Maat et al., 2007). In addition to the biological impact that the acute disease of MSS has on the child, the disease also exposes both children and their parents to an overwhelming amount of emotional distress and has a profound emotional impact on them.

A few studies have been conducted into the short-term psychological outcome of Meningococcal Disease (MD) in children and adolescents. These studies showed high rates of post-traumatic stress symptoms in patients as well as in their parents (Fellick et al., 2001; Judge et al., 2002; Shears et al., 2005; Shears et al., 2007). Fellick et al. found poorer cognitive and behavioural functioning in 8-25 year-old MD patients compared to a control group, 8-10 years after the disease (2001). However, these studies into MD used heterogeneous samples, encompassing meningitis, septicaemia or both (MSS).

Our research group was the first to investigate systematically both the medical and psychosocial outcomes in a homogeneous sample, consisting only of patients who survived MSS, on the long-term. Patients with MSS show the clinical features of meningitis but in addition the cardiovascular collapse of a septic shock causing a more fulminant illness with a higher mortality rate. We found that long-term outcomes as to behavioural, emotional and posttraumatic stress problems in children and adolescents, 4 to 16 years after MSS, were comparable to those in the reference population (Vermunt et al., 2008). A trend, however, towards more problems with increasing age was found. Also a similar, significant, age-effect in child and adolescent MSS survivors towards more cognitive problems with increasing age, long-term after MSS, was found (Vermunt et al., submitted). Considering these trends towards more cognitive, behavioural and emotional problems with increasing age in our child and adolescent MSS samples, we hypothesized that patients, who are adults at present and have survived MSS in childhood, will show long-term psychosocial problems. No study has yet investigated the long-term psychosocial outcome in adults, who survived MSS during childhood. The aims of the present study were:

1. To examine the biographical characteristics and illness-related physical or social consequences in adults who survived MSS.

2 To compare the level of intellectual functioning in adults who survived MSS with that of a normative reference group.
3. To compare the levels of behavioural and emotional problems in adults who survived MSS with those of a normative reference group.
4. To evaluate the predictive value of age at time of illness, severity of illness, age at time of follow-up and gender separately on the level of intellectual functioning and on the level of behavioural and emotional problems.

Methods

Instruments

Semi-structured interview

A semi-structured interview (with pre-coded items) developed for this study was used to investigate biographical characteristics and to examine illness-related physical or social consequences in adults who survived MSS (see Tables 1 and 2).

Groninger Intelligence Test 2 (GIT2)

A Dutch standardized intelligence test, the Groninger Intelligence Test 2 (GIT2), was used to assess intellectual functioning (Luteijn & Barolds, 2004). In this study a shortened version of the GIT2 was used, based on 6 subtests: Verbal Comprehension, Visualization, Closure, Number, Reasoning/Induction/Deduction and Word Fluency. The psychometric properties of the GIT short form (reliability, validity) have been proven to be between satisfactory and good (Luteijn & Barolds, 2004).

Adult Self-Report (ASR)

The Adult Self-Report (ASR) (Achenbach & Rescorla, 2003) was used to obtain standardized self-reports of behavioural and emotional problems in adults aged 19-31 years. The problem section consists of 126 problem items. Adults rate their behaviour during the preceding six months on a 3-point scale (0 = not true; 1 = somewhat or sometimes true; 2 = very true or often true).

The ASR consists of 8 specific syndrome scales and two broad problem areas: Internalizing and Externalizing. The Internalizing scale consists of the syndrome scales Withdrawn, Somatic Complaints and Anxious/Depressed, whereas the Externalizing scale consists of Rule-Breaking, Aggressive Behaviour and Intrusive. The syndrome scales Thought Problems and Attention Problems belong neither to the Internalizing nor the Externalizing scale. A Total Problems score can be obtained by summing the scores on all individual problem items. A higher score indicates a higher level of problems.

Moderately high internal consistency and high reliability of ASR have been established (Achenbach & Rescorla, 2003). A Dutch translation of the ASR was available. The ASR internalizing and externalizing broadband scales had high internal consistency, with Cronbach's alphas of 0.93 and 0.87 respectively (Vanheusden et al., submitted).

Medical variables

The Paediatric Risk of Mortality (PRISM) score, a validated score to express the severity of illness, was used as index of severity of illness (Pollack et al., 1988). The score is calculated on the basis of the most abnormal values for physiological variables during the first 24 hours of admission to an Intensive Care Unit.

Description of the samples

Inclusion and exclusion criteria

During the follow-up, which took place in 2005-2006, consecutive surviving patients with a clinical picture of meningococcal septic shock (MSS) requiring intensive care treatment at the PICU of ErasmusMC-Sophia Children's Hospital at least four years ago (between 1 August 1988 and 1 June 2001) were eligible. In this study MSS is defined as septic shock with petechiae/purpura. For the detailed description of septic shock see Joosten et al. (2000). In 83% of the patients *Neisseria meningitidis* was cultured in the blood. In addition, in half of the patients a lumbar puncture was performed: in 90.9% *Neisseria meningitidis* was also cultured in liquor or pleiocytosis was present in case of negative culture, which indicates presence of meningitis. Patients who were not Dutch speaking were excluded.

Patient sample

The target population comprised of 179 consecutive surviving patients. At follow-up 9 patients were lost (7 moved abroad, 1 deceased and 1 untraceable). Of the remaining 170 patients, 83 patients, aged 16-31 at follow-up (age range used in this study) were eligible. Of these 83 patients, 44 patients were aged 19-31 years. The median follow-up interval was 13 years, with a range of 4-16 years. The final study sample consisted of 58 patients (28 male, 30 female, response rate 69.9%), who had had MSS before 18 years of age.

Twenty-five patients refused to participate on practical grounds (too much time, n=7), emotional grounds (n=6) or unknown reasons (n=12). Statistical test showed that non-participating patients were significantly younger at time of illness (mean age: 5.8 years old) than participating patients (mean age: 9.2 years old). Non-participating patients were also significantly younger at time of follow-up (mean age: 18.9 years old) than participating patients (21.5 years old). The participating and non-participating patients did not differ significantly in regard to severity of illness and gender. Ten patients completed the questionnaires at home and did not want to come to the hospital for the intelligence test because of practical reasons.

For different instruments, different age-ranges were used. Therefore the number of patients and response rates differ. The final study sample consisted of the following sub samples:

1. Biographical characteristics and illness-related physical or social consequences: 56 16-31-year old patients underwent the semi-structured interview (response rate: 56/83×100%: 67.5%).
2. Intellectual functioning: 46 16-31 year-old patients underwent the IQ-test (response rate: 46/83×100%: 55.4%).
3. Behavioural and emotional problems: in total 37 19-31 year-old patients filled in the ASR questionnaire (response rate: 37/44×100%: 84.1%).

Reference groups

Data from the patient sample were compared with data derived from large representative Dutch normative samples from the general population, with comparable age-ranges, assessed with the same instruments.

1 For the biographical characteristics marital status, occupational status, educational level and sick leave, recent normative data were derived from a variety of very large, and thus representative samples from the Central Bureau of Statistics (CBS). Normative data were, wherever available, specified by age (CBS, 2007). To prevent confusion, sample sizes of different very large reference groups were not indicated in Table 1.

2 For the GIT 2, Dutch norms for different age-categories were available based on a normative sample of 1514 persons (Luteijn & Barolds, 2004).

3 For the ASR, a Dutch normative sample of 2245 persons within the age range of the MSS sample was available (Vanheusden, in press).

Assessment procedure

The research protocol was approved by the ethics committee review board before the start of the study. All patients were traced, approached uniformly and signed an informed consent before participating in the study. The psychological investigation took place in the department of Child and Adolescent Psychiatry in the ErasmusMC-Sophia Children's Hospital. Two weeks before the psychological investigation, patients were sent the ASR to complete it at home and bring it with them to the psychological investigation. Ten patients did not undergo the tests for cognitive functioning and were prepared to complete the questionnaires at home and return them with a prepaid envelope.

Statistical analyses

All analyses were performed with two-sided tests; $p<0.05$ was considered significant.

Biographical characteristics: For biographical characteristics, proportions of MSS patients were compared with proportions of same-aged reference persons by Binomial Exact Testing.

Cognitive functioning: One sample t-tests were used to test differences in group means on intellectual functioning between the MSS sample and a normative reference group.

Behavioural and emotional problems: To distinguish problem adults from non-problem adults, the 90th percentiles of the cumulative frequency distribution of the ASR Total Problem scores obtained for the reference group were chosen as the cut-offs. Due to gaps between rank ordered scores, the percentages from the reference groups scoring above the 90th percentile were not exactly 10%. Differences in proportions scoring in the deviant range between patient samples versus reference groups were analyzed by Binomial Exact Testing. Differences in mean scores of the patient sample versus the reference group were assessed with analyses of covariance (AN(C)OVAs). Educational level (8 categories) was partialled out as covariate since the distribution of educational level of the patient sample differed significantly from that of the reference group ($\chi^2 = 16.3$, df = 7, $p<0.01$), with middle educational levels being represented more, and higher educational levels being represented less, in the MSS patient sample compared to the reference group.

Prediction: To examine the predictive value of age at time of illness, severity of illness, age at time of follow-up and gender separately on intellectual functioning and on behavioural and emotional problems, the method of multiple regression analysis was applied. Depending on whether follow-up interval (4-16 years) made a significant contribution to the regression models, adjustment for this variable was applied on the linear regression analyses (for details: see Results). In literature it has been described that the incidence of meningococcal disease was associated with socio-economic deprivation across a rural English region (Stuart et al., 2002). In our patient sample also a large proportion of persons with a low or middle SES level exist (highest SES level of both parents at time of follow-up; SES level 1: 34.5%; SES level 2: 40.0%; SES level 3: 25.5%). When SES level made a significant contribution to the regression models, then it was adjusted for in the linear regression analyses.

Results

Biographical characteristics and illness-related physical or social consequences

Table 1 shows that about half of the patient sample (55%) was living with their parents or another care-taker. Regarding the offspring, 93% of the patient sample had no children. Furthermore 94% of the patient sample did not feel the MSS to be a limiting factor for the choice of having offspring. The vast majority (95%) had regular daily activities; school attendance, a paid job or a combination of both.

Table 1 also shows that, when specified for age categories, no significant differences in marital status were found between the patient samples and the reference groups.

Table 1. Biographical characteristics of the patient sample and of the reference group.

	Patient sample			
	N	%		
Living conditions (n=56) [a]				
With parents or another care-taker	31	55.4		
Living independently	24	42.9		
In institution (prison)	1	1.8		
Offspring (n=56) [a]				
0	52	92.9		
1	3	5.4		
2	1	1.8		
MSS limiting factor for choice of having offspring (n=56) [a]				
No	47	94		
Yes	3	6		
Daily activities (n=56) [a]				
Attending school	24	42.9		
Job	26	46.4		
Combination school and job	3	5.4		
Disablement pension [b]	1	1.8		
Labour institution for mentally handicapped	1	1.8		
Other: in prison	1	1.8		
	Patient sample		**Reference**	**P-value**
	N	**%**	**group %**	
Marital status 15-20 years (n=23) [c]				
Not married (no relationship, stable relationship, cohabitant)	23	100.0	99.7	ns
Married	0	0.0	0.3	ns
Marital status 20-25 years (n=21)				
Not married (no relationship, stable relationship, cohabitant)	20	95.2	93.5	ns
Married	1	4.8	6.5	ns
Marital status 25-30 years (n=11) [d]				
Not married (no relationship, stable relationship, cohabitant)	8	72.7	75.3	ns
Married	3	27.3	24.7	ns
Occupational level 15-34 years (n=26) [e]				
1	1	3.8	8.7	ns
2	7	26.9	26.6	ns
4	13	50.0	38.8	ns
6	4	15.4	18.8	ns
8	1	3.8	7.2	ns
Sick leave (n=26)				
Mean sick-leave percentage [f]	3.5	(SD: 8.0)	4.0	ns
Sick leave according to patients				
Less than colleagues	19	73.1		
Equal to colleagues	4	15.4		
More than colleagues	3	11.5		
Reason sick leave				
Unrelated to MSS	13	92.9		
MSS the only reason	1	7.1		

Table 1. Continued

	Patient sample N	Patient sample %	Reference group %	P-value
Educational attainment 15-24 years (n=44) [c]				
Lower	22	50.0	53.3	ns
Average	14	31.8	38.6	ns
Higher	8	18.2	8.1	0.02
Educational attainment 25-44 years (n=13) [g]				
Lower	2	15.4	22.8	ns
Average	5	38.5	45.9	ns
Higher	6	46.2	31.3	ns

[a] : for these variables no normative data was available

[b] : considered to receive social security benefits

[c] : data of 15-year-old MSS patients were not available

[d] : 31-year-old MSS patients were excluded (n=1)

[e] : only data of 16-31 year-old MSS patients were available

[f] : Sick-leave percentage was used instead of number of days on sick-leave, since the number of hours a person works a week (full-time/part-time) might vary considerably

[g] : only data of 25-31 year-old MSS patients were available

ns: not significant

With respect to occupational status no significant differences were found between the patient sample and the reference group. It has to be taken into account that the numbers were based on only persons with a paid job (n=26).

The mean sick-leave percentage of the MSS patients was not significantly different from that of the reference group. This was not in accordance with the patients' own perception, since 73% of the patient sample reported to have a lower sick leave than colleagues.

Regarding educational attainment, overall no significant differences were found between educational levels of the patient sample and those of the reference group.

Table 2 shows that the vast majority of the patient sample (92%) did not feel disadvantaged because of the MSS and did not have the feeling that they could perform physically less than they would have wanted during the last month (85% of the patient sample). A minority of the patient sample (15.3%, n=8) did express the feeling to have less physical capacities due to the MSS.

26.8% Of the patient sample reported that people could tell that they had had MSS, based on their physical appearance (all these patients had scars). Eighty percent of those patients were never hold back because of this.

In the semi-structured interview 44% of the patients reported to have scars. A minority (9%, n=2) of them reported to be dissatisfied with how they look.

Intellectual functioning

Table 3 shows that the patient sample obtained a mean total IQ score comparable to that of the reference group. On the subtests Verbal Comprehension, Number and Word Fluency

Table 2. Illness-related physical or social consequences

	Patient sample	
	N	%
Overall, since the MSS, how much of a disadvantage you feel you have compared to others your age?		
No disadvantage	45	91.8
Somewhat disadvantaged	2	4.1
Strong disadvantage	2	4.1
How many times in the last month did you feel that physically you could do less than you would have wanted, because of the MSS?		
Never	44	84.6
Sometimes	6	11.5
Often	2	3.8
If so, how much does it bother you?		
Not	1	14.3
A bit	4	57.1
Very much	2	28.6
Based on your physical appearance, can people tell that you had MSS (i.e. scars, one leg longer than the other)?		
No	41	71.7
Yes	15	26.8
If yes, did this hold you back or make things difficult for you?		
Never	12	80.0
Sometimes	2	13.3
Often	1	6.7
Do you have any scars as a result of the MSS?		
No	29	55.8
Yes	23	44.2
If so, are you satisfied, not really satisfied or dissatisfied, or dissatisfied with how you look?		
Satisfied	14	60.9
Not satisfied/ not dissatisfied	7	30.4
Dissatisfied	2	8.7

the patients obtained scores that were significantly lower than those of the reference group (respectively $p<0.05$, $p<0.05$ and $p<0.001$). On the subtest Closure (assessing gestalt completion) higher scores were obtained by the patients ($p<0.01$). The differences on the subtests Word Fluency and Closure remained significant after Bonferroni's correction for multiple independent testing.

Behavioural and emotional problems

Table 4 shows the proportions of MSS adults and reference adults scoring in the deviant range for problem behaviour. Overall, no significant differences were found between the proportions of MSS patients and those of reference adults (with same age and gender) scoring in the deviant range. The exception was that the proportion of MSS males (aged 19-23 years; n=9) scoring in the deviant range was significantly greater than that of same-aged males in the reference group ($p=0.01$). This difference remained significant after Bonferroni's correction.

Table 3. Cognitive functioning of the patient sample and reference group.

	MSS		Reference group		
	Mean	**SD**	**Mean**	**SD**	**P-value**
GIT 2 IQ	96.2	13.9	100.0	15	0.07
Verbal Comprehension	4.7	1.9	5.3	2	<0.05
Visualization	5.6	2.1	5.2	2	0.25
Closure *	5.9	1.9	5.1	2	<0.01
Number	4.4	2.2	5.1	2	<0.05
Reasoning/Induction/Deduction	4.8	2.1	5.3	2	0.09
Word Fluency *	4.0	1.6	5.1	2	<0.01

* Significant difference after Bonferroni's correction.

Table 4. Percentages of MSS sample and reference group scoring in the deviant range for problem behaviour

	ASR				
	Mean Total Problems scores		% > Cut-off		Binomial Test *P*
	MSS (n)	**Reference (n)**	**MSS**	**Reference**	
Males[a]					
19-23	55.7 (9)	38.0 (358)	44.4	10.6	0.01*
24-30	37.9 (9)	36.1 (603)	0	10.3	ns
Females[a]					
21-23	37.4 (10)	44.8 (299)	20.0	10.0	ns
24-31	27.1 (10)	37.9 (771)	0	10.1	ns
Total sample	41.4 (37)	38.9 (2230)	16.2	10.1	ns

[a] Age categories based on the median split of patient samples.

* Significant difference after Bonferroni's correction.

Ns not significant

To test differences in mean total problem scores and mean scale scores, ANCOVA's were computed with educational level partialled out as a covariate. No significant differences were found between the mean scale scores on any of the ASR-scales for the MSS patient sample and reference group.

Prediction

For the prediction of intellectual functioning, no adjustment for follow-up interval was applied since follow-up interval did not have a significant unique contribution to the regression analyses. SES level was adjusted for since it had a significant contribution to the regression analysis for several IQ subtests.

Age at time of illness, severity of illness, age at time of follow-up and gender were no significant predictors for the total IQ outcome or any of the IQ subtests.

As to the prediction of behavioural and emotional problems, adjustment for follow-up interval was applied, since follow-up interval had a significant contribution to the regression

Table 5. Prediction of behavioural and emotional problems.

	b	Standard error *b*	*P* value	Multiple R
Age at time of illness				
Externalizing	-2.50	0.44	0.02	0.51
Rule-Breaking Behaviour	-0.81	0.16	0.01	0.44
Age at time of follow-up				
Externalizing	-0.86	0.40	0.04	0.50
Rule-Breaking behaviour	-0.35	0.15	0.03	0.41
Gender				
Total Problem Score	-16.35	6.39	0.02	0.58
Externalizing	-4.98	2.41	0.05	0.49
Intrusive	-1.59	0.73	0.04	0.37
Rule-Breaking Behaviour	-2.22	0.89	0.02	0.42
Attention Problems	-3.82	0.21	0.01	0.42
Withdrawn	-1.46	0.66	0.04	0.42

ASR scale scores: adjustment for follow-up interval, no adjustment for SES level

analyses. SES level did not have a significant contribution, so no adjustment for SES level was applied.

Age at time of illness was a significant predictor for Externalizing problems scores and Rule-Breaking behaviour (Externalizing: $p<0.05$; Rule-Breaking Behaviour: $p<0.01$)(see Table 5). Younger age at time of illness was associated with higher scores on Externalizing and Rule-Breaking Behaviour. Age at time of follow-up was a significant predictor for the same two scales; Externalizing and Rule-Breaking Behaviour (both $p<0.05$). Younger age at time of follow-up was associated with more problems on these scales. Gender was a significant predictor on the following scales: Total, Externalizing, Intrusive, Rule-Breaking Behaviour, Attention Problems and Withdrawn (all $p<0.05$, except Attention Problems: $p<0.01$). Male gender was associated with more problems on these scales. Severity of illness was no significant predictor on any of the ASR scales.

Discussion

Biographical characteristics and illness-related physical or social consequences

Our most important finding is that despite the severe MSS in childhood, adults appear to function well and lead normal lives as regards living conditions, having offspring, daily activities, marital status, occupational status and educational attainments.

Sick leave percentage for the MSS sample was not different from that of the reference group, but a majority of the MSS sample (73%) estimated that their sick leave was less than that of colleagues. A possible explanation for this might be that the patients may tend to ‘overcompensate’ their former illness; they may tend to make up for feelings of inferiority or vulnerability, for example by reporting a lower sick leave. Another possibility might be that patients may have given social desirable answers.

Remarkably 92% of the patient sample did not report to feel physically or socially disadvantaged because of the MSS whereas almost half of the patients reported to have scars. The majority of patients with scars reported to be satisfied with their appearance. This is in line with our previous study (Vermunt et al., 2008) in which no differences were found between MSS children and adolescents with and without scars as to how they perceive themselves on physical appearance. The present 'positive' findings are also in line with positive results of two studies into psychological outcome in patients with burns (Baker et al., 2007; Pope et al., 2007). In these studies the burns were on 1-63% and 30-99% of the total body surface. MSS patients generally have few scars in the facial area. Despite the fact that the place and extent of scars may differ between MSS and burn survivors, the psychological outcomes point in a similar direction.

Cognitive functioning

Overall, results of the total MSS sample as to intellectual functioning were similar to those of a normative reference group, though a non-significant trend towards a lower IQ was found. As far as we know, no study has yet focussed on long-term cognitive functioning in MSS patients at adult age. In 2 recent reviews it was concluded that critical illness at an adult age and admission to an ICU has negative cognitive consequences (Gunther et al., 2007; Hopkins et al., 2007). Neurocognitive impairments are extremely common in survivors of critical illness at an ICU (25-78% of ICU survivors experience neurocognitive impairments) and affect a variety of cognitive domains (Hopkins et al., 2007). Deficits in memory are observed most frequently, followed by deficits in executive function and attention. These neurocognitive impairments generally improve during the first 12 months, but significant and persistent deficits after 2 to 6 years have been reported (Hopkins et al., 2007). The previous studies encompassed different patient samples (including patients with Acute Respiratory Distress Syndrome, acute lung injury, respiratory failure, medical ICU patients, surgical operations and general ICU patients), follow-up intervals were mainly shorter than 2 years and patients became ill at adult age. Though results are difficult to compare due to different patient samples, time intervals and different ages at onset of illness, we think attention should be paid to screening and identifying patients at risk for cognitive problems, after critical illness at an ICU.

Behavioural and emotional problems

Overall, levels of behavioural and emotional problems of MSS patients were comparable to those of reference adults from the general population. These results are in line with positive outcomes of 2 previous studies by our research group into long-term psychological outcome in MSS children and adolescents and health-related quality of life (HR-QoL) in the same adult sample as used here (Vermunt et al., 2008; Buysse et al., 2007). In the previous studies we gave as possible explanation that the 'favourable' results might reflect resilience. This explanation may also apply to our present findings for MSS adults. After a life-threatening illness as MSS, ex-patients may be more inclined to appreciate and enjoy life more.

Only one study investigated long-term psychological outcome in MD patients (Fellick et al., 2001). This study showed that MD patients aged 8-25 years performed at a lower level on measures of behaviour than controls; they had more cognitive problems, global problems and problems on ADHD measures, 8-10 years after MD (Fellick et al., 2001). Results are difficult to compare, however, since in the study of Fellick et al. a heterogeneous and younger patient sample was used than in our study.

Several studies have shown negative psychological outcomes as to anxiety, depression, PTSD, psychological distress and HR-QoL shortly after ICU admission during adulthood. In these studies mainly heterogeneous patient samples were used, focussing on short-term outcomes (<4 years) with different time-intervals and different outcome measures (Perl et al., 1995; Heyland et al., 2000; Eddleston et al., 2000; Griffiths et al., 2007; Sukankarat et al., 2007; Erickson & Martin, 2008).

Overall, in the study of Fellick et al. (2001) and in the studies into ICU outcome negative psychological outcomes were found, whereas in the present study no negative psychological outcomes were found. The contradictory results may be due to the longer follow-up interval (4-16 years) and the homogeneous patient sample that was used in the present study. Our present long-term outcomes seem to indicate that at long-term, life has become normal and behavioural and emotional problems are no longer present.

Prediction

As to long-term intellectual functioning, age at time of illness, age at time of follow-up, severity of illness and gender were no significant predictors. But as to long-term behavioural and emotional problems (especially externalizing problems), younger age at time of illness, younger age at time of follow-up and male gender were significant predictors. Overall, however, MSS patients obtained scores for behavioural and emotional problems that were within the normal range, in comparison with a normative reference group. Thus these predictors only predict worse outcomes within the patient sample.

Both in this study with MSS adults as in our previous study with MSS children and adolescents severity of illness was no predictor for behavioural and emotional problems. In two recent studies into psychological outcome of ICU admission at adult age, in heterogeneous samples, it has also been found that severity of illness was not associated with behavioural and emotional problems such as PTSD, anxiety, depression, intrusion and avoidance behaviour (7 days to 8 years after discharge) (Griffiths et al., 2007; Sukankarat et al., 2007).

In our previous study with MSS children and adolescents male gender was also found to be a significant predictor of behavioural and emotional problems. Therefore, results are in line. From the general population it is also known that male gender is a risk factor for externalizing problems (Achenbach & Rescorla, 2003). In addition, in the present study male gender was also associated with other problem areas.

Strengths and limitations

Long-term psychosocial outcome in adult survivors of MSS in childhood has not been investigated before. A unique feature of this study is the homogeneous patient sample of adult MSS survivors.

This study has been done in one centre, and question marks can be set at generalizability to other centres. Future research should be done in multiple centres. The response rate was satisfactory, but to what extent missing data has influenced our results is unknown.

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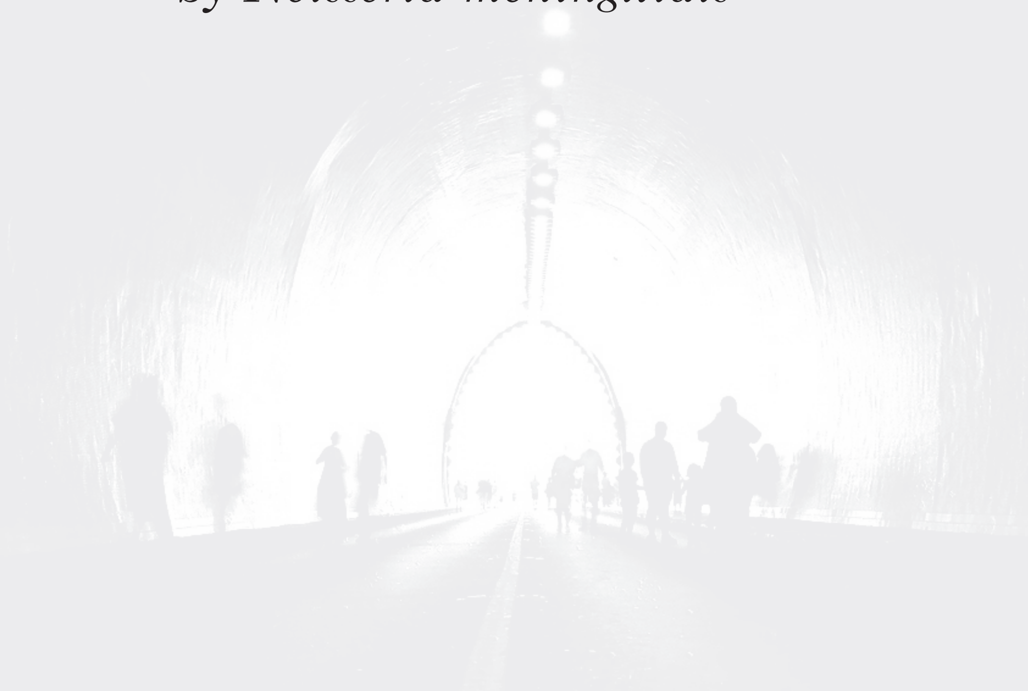
6

Overcoming the odds: favourable long-term outcomes on mental health and disease-specific limitations in parents of children and adolescents who survived septic shock caused by *Neisseria meningitidis*



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Abstract

Aims

To investigate mental health and disease-related psychosocial limitations in parents of children and adolescents who survived Meningococcal Septic Shock (MSS) 4 to 16 years ago.

Methods

The General Health Questionnaire was used to assess mental health and a semi-structured interview to explore long-term disease-specific limitations for parents.

Results

Parents reported less psychiatric symptoms compared to reference groups. Severity of illness and age at time of illness were no significant predictors of parental mental health.

The vast majority of parents reported no current psychosocial limitations due to the MSS. Seven percent of the parents decided not to have more children because of the MSS. One tenth of the parents reported that the current emotional burden because of the MSS is large.

Conclusion

Overall favourable long-term outcomes were found in parents of children who survived MSS. Nevertheless a minority of parents still experiences current emotional burden and disease-related limitations.

Introduction

Septic shock in children, predominantly caused by *Neisseria meningitidis*, is a life-threatening illness that has an abrupt onset and a fulminant course. Despite advances in knowledge about pathophysiology and treatment, morbidity and mortality remain high (19% Baines, 2003; 15.7% Maat et al., 2007). The clinical presentation of MSS is often dramatic with death potentially ensuing in a matter of hours. A previously 'normal, healthy' child becomes suddenly very ill, is fastly admitted to a Paediatric Intensive Care Unit (PICU), and children and their parents are exposed to an overwhelming amount of emotional distress. One study, describing the experiences of parents of children who suffered meningococcal disease, concluded that living through this experience is perceived as a major stressor (Haines, 2005). She found that the transition from the role of 'parent of a healthy child' to 'parent of a critically ill child', feelings of helplessness and guilt were major sources of stress. Parents may be extremely emotional, feel vulnerable and may disbelieve what is happening. Fear about a possible death and uncertainties about possible physical or mental outcome after survival elevates the stress and anxiety levels. Parents are often overwhelmed and shocked by the invasive treatment measures and the changed appearance of their child is very upsetting. Children with MSS are one of the most severely ill and unstable groups of children admitted to a PICU and it may be clear that when a child gets MSS, it places an immense burden on the child and its parents (Haines, 2005). For the parents, the MSS period of their child can be considered a traumatic event.

Until now, no study has investigated the short- and long-term consequences for parents of children who survived septic shock. Three studies have focused on short-term consequences of a heterogeneous group called meningococcal disease, consisting of meningitis, septicaemia or both. In these studies with a short-term follow-up ranging from 3 to 12 months after admission to the PICU, prevalence of psychiatric symptoms was found in 42-69% of mothers and in 24-58% of fathers (Judge et al., 2002; Shears et al., 2005; Ehrlich et al., 2005). Risk for Post-Traumatic Stress Disorder (PTSD) was found in 38-48% of mothers and in 19% of fathers (Judge et al., 2002; Shears et al., 2005). A limitation in these studies was that they did not differentiate between the severity of disease; they used heterogeneous samples containing patients with sepsis, septic shock or meningitis.

As far as we know, only one study investigated long-term consequences of meningococcal disease in parents. In this study, using five small cross-sectional subgroups of patients assessed at different time-intervals (3 months up to 36 months or longer after discharge from the PICU), a prevalence of psychiatric symptoms comparable to the general population 3 years or more after discharge, both in mothers and fathers was found (Ehrlich et al., 2005). Again in this study no distinction was made between the severity of diseases and data were not gathered in a standardized manner (parents completed questionnaires at home).

Since no previous study has investigated the long-term outcome of specifically Meningococcal Septic Shock (MSS), the most severe form of meningococcal disease, on the levels of psychiatric symptoms and disease-related psychosocial limitations in parents, this study was undertaken. Parents of a homogeneous sample, consisting of only children who survived MSS, between 1988 and 2001, participated in this study. Outcomes of mothers versus fathers were compared, since previous studies into short-term outcomes in meningococcal diseases indicated gender differences in parental outcomes (Shears et al., 2005; Ehrlich et al., 2005). Furthermore, the predictive value of severity of illness on psychiatric symptoms was investigated, since one study found that severity of illness at time of admission was associated with higher mothers' PTSD symptom levels at 3-12 month follow-up (Judge et al., 2002). In addition the predictive value of age of the child at illness was investigated. No previous study has studied long-term disease-related limitations (such as limited possibility to go out or going on holiday) for parents; therefore these variables were explored in this study. The aims of the present study were:

1. To compare the levels of psychiatric symptoms of mothers and fathers of children and adolescents who survived MSS with those for men and women in reference groups.
2. To compare the level of psychiatric symptoms of mothers versus fathers from the patient sample.
3. To examine the predictive value of severity of illness and age of the child at time of illness separately on psychiatric symptoms of the parents.
4. To explore present disease-related psychosocial limitations for parents of MSS survivors.

Methods

Instruments

General Health Questionnaire (GHQ)

The 28-item version of the GHQ was used, a standardized self-report to assess mental health (Goldberg & Hillier, 1979). The good reliability and validity of the GHQ were replicated for the Dutch version (Koeter & Ormel, 1992). The GHQ contains four scales, which are concerned with somatic symptoms, anxiety and sleeplessness, social dysfunctioning and serious depression. The range of scores for the Likert scoring (0,1,2,3) that was used for comparisons of mean scores is 0-84. To determine the proportions of mothers and fathers at risk for psychiatric disorder, cases with scores above the recommended and internationally used cut-off (a score of 5 or more on the total score, using the GHQ-scoring of 0 and 1, range of scores: 0-28) (Goldberg & Williams, 1988; Koeter & Ormel, 1992; Shears et al., 2005) were assessed. Persons scoring above this cut-off show clinically elevated levels of psychiatric symptoms.

Semi-structured interview

A semi-structured interview (with pre-coded items) developed for this study was used to assess present, disease-related psychosocial limitations in parents of MSS survivors.

PRISM-score

The Paediatric Risk of Mortality (PRISM) score, a validated score to express the severity of illness, was used as index of severity of illness (Pollack et al., 1988). The score is calculated on the basis of the most abnormal values for physiological variables during the first 24 hours of admission to an Intensive Care Unit.

Description of the sample

Inclusion and exclusion criteria

During the follow-up, which took place in 2005-2006, consecutive surviving patients with a clinical picture of meningococcal septic shock, defined as septic shock with petechiae/purpura, requiring intensive care treatment at the PICU of ErasmusMC-Sophia Children's Hospital 4 to 16 years ago (between 1 August 1988 and 1 June 2001) were eligible. In 83% of the patients *Neisseria meningitidis* was cultured in the blood. In this paper this will be called MSS further on. Parents and patients who were not Dutch speaking were excluded.

The present study included parents of 6 to 17 year-old children.

Patient and parent sample

The target population of the present study consisted of parents of 109 consecutive surviving patients in the age-range of 6 to 17 years. At follow-up, 5 patients were lost (4 moved abroad and 1 deceased). Twelve sets of parents refused to participate on practical or emotional grounds (for example no time because of a busy job, or a new confrontation with the hospital was considered too emotional). For the remaining 92 patients, 4 parents provided incomplete questionnaires, which were excluded from statistical analyses. The final sample consisted of parents of 88 children (76 sets of both parents, 11 mothers alone and 1 father alone). The response rate (corrected for deceased persons and persons lost to follow-up) for mothers was 84% and for fathers was 74%. Next to completing the GHQ, parents (fathers, mothers or both parents together) of these 88 MSS survivors were interviewed.

Significant differences were found between the mean ages of mothers (40.1 years, SD= 5.1) and fathers (43.2 years, SD= 6.2) in the present patient sample.

Socio-economic status (SES) was scored on a 9-point scale of parental occupation, with scores 1 to 3 corresponding with elementary and so called 'lower' occupations (SES-level 1), 4 to 5 corresponding with so called 'middle' occupations (SES-level 2) and 6 to 9 corresponding with so called 'higher' and scientific occupations (SES-level 3) (See Table 1) (Netherlands Central Bureau of Statistics, 2001).

Table 1. Characteristics of patient and parent sample

	General Health Questionnaire	
	N	**(%)**
Age distribution of patients		
6-11 year	50	(57%)
12-18 year	38	(43%)
Gender distribution		
Boys	45	(51%)
Girls	43	(49%)
Socio-economic status[*]		
SES-level 1	31	(35%)
SES-level 2	40	(46%)
SES-level 3	17	(19%)
Total	88	(100%)

Abbreviations: SES: socio-economic status

Reference groups

Normative data were derived from the manuals of the questionnaires used. The reference groups for the GHQ consisted of representative random samples drawn from the Dutch general population (Koeter & Ormel, 1992).

The disease-related questions regarding present psychosocial limitations for parents were developed specifically for this study's aim, therefore no normative data are available.

Assessment procedure

Before the start of the study, the research protocol was approved by the ethics committee review board. All parents (and their children) were traced, approached uniformly and signed an informed consent before participating. During the psychological investigation of their child in the department of Child and Adolescent Psychiatry of ErasmusMC-Sophia Children's Hospital, the psychologist interviewed parents of 6 to 17 year-old children. After being instructed they completed the questionnaire, independently of each other, in the waiting room. Most children were accompanied by two parents. When one parent accompanied the child, the accompanying parent was asked, if possible, to deliver the questionnaires to his/her partner, who could complete them at home and return them with a prepaid envelope.

Statistical analyses

All analyses were performed with two-sided tests; $p < 0.05$ was considered significant. One-sample t-tests were used to test differences in group means between the parents of the present patient sample and reference groups on the GHQ. Differences in proportions scoring above cut-off between mothers and fathers versus respectively reference females and males were analyzed by Binomial Testing.

To identify the role of gender (boys versus girls) and age (5-11 years versus 12-18 years) within the parent sample, univariate analyses of (co)variance, AN(C)OVAs, were performed on all scales of the GHQ. The variable socio-economic status (SES: 3 levels) showed a significant main effect in ANOVAs on three of four scales of the GHQ filled in by mothers indicating more psychiatric symptoms in lower SES classes; this effect has also been described for the general population (Koeter & Ormel, 1992; Reijneveld & Schene, 2001; Belek, 2000). It was decided to apply SES as covariate in analyses on this questionnaire.

Differences in means on the GHQ between mothers and fathers within families were assessed with paired t-tests. To examine the predictive value of severity of illness and age at time of the child at time of illness separately on psychiatric symptoms in parents, regression analyses were performed. Depending on whether follow-up interval (4-16 years) and socio-economic status (SES:3 levels) separately made a significant contribution to the regression models, adjustment for these variables was applied on the linear regression analyses. As to the prediction of psychiatric symptoms in mothers and fathers separately, no adjustment for follow-up interval (4-16 years) was applied, since follow-up interval did not made a significant contribution to the regression model. Socio-economic status (SES: 3 levels) was adjusted for in the prediction of psychiatric symptoms in mothers.

Results

Comparison of psychiatric symptoms of the parent sample versus reference groups

Table 2 shows that, compared to reference females, mothers of children who survived MSS reported significantly less complaints on the GHQ scales concerning somatic symptoms, anxiety and sleeplessness and serious depression. Fathers reported significantly less complaints than reference males with regard to somatic symptoms and anxiety and sleeplessness. All results remained significant after Bonferroni corrections for 5 comparisons (p<0.01).

Proportions of cases at risk for psychiatric disorder in the parent sample versus reference groups

Percentages of mothers and fathers of children who survived MSS having scores above the cut-off score of 5 or more on the GHQ-total score (Shears et al., 2005; Koeter & Ormel, 1992) were calculated. Twenty-four percent of 87 mothers and 22% of 76 fathers of children who survived MSS obtained a score of 5 or more on the GHQ. The proportions of mothers and fathers of MSS survivors scoring above cut-off were significantly smaller compared to those of respectively reference females and males scoring above the same cut-off (p< 0.01).

Table 2. Mean scores on the General Health Questionnaire of parents of children who survived MSS and the reference group

	Parents of MSS children				Reference	
			Couples			
	Mothers (n=87)	Fathers (n=77)	Mothers (n=76*)	Fathers (n=76*)	Females (n=258)	Males (n=216)
Scales	**Mean**	**Mean**	**Mean**	**Mean**	**Mean**	**Mean**
Somatic symptoms	4.9[1]	4.2[1]	4.9[1]	4.2[1]	6.7[1]	5.4[1]
Anxiety and sleeplessness	4.7[1]	4.0[1]	4.4[1]	3.9[1]	6.0[1]	5.5[1]
Social dysfunctioning	6.9	7.3	6.9	7.2	6.9	7.1
Serious depression	1.1[1]	1.3	1.1[1]	1.4	1.6[1]	1.5
Total score	4.4	4.2	4.3	4.2	4.7	4.0

A high total score and high subscale scores are indicative of unfavourable functioning.

[1] Significant ($p<0.05$) difference (after Bonferroni correction) between MSS mothers or fathers versus same-sex reference groups

[*] For 76 MSS parent couples, data were available from both parents.

Comparison within MSS families: mothers versus fathers

Table 2 also shows the mean scores for couples of parents of the patient sample.

On the GHQ no significant differences were found between mothers versus fathers in the present patient sample.

Effect of gender and present age of children

No main effect of gender and no main effect of current age of the children were found on any of the GHQ-scale scores or the total score, nor for mothers nor for fathers.

Predictive value of severity of illness and age of the child at time of illness on psychiatric symptoms

Severity of illness (PRISM), and age of the child at time of illness, were no significant predictors for any of the GHQ scale scores or the total score, neither in mothers and fathers, apart from 1 exception. A significant negative relationship was found for fathers between severity of illness and anxiety and sleeplessness (p=0.01).

When selecting only the fathers, respectively only the mothers, who scored above the cut-off of the GHQ-total score (indicating risk for psychiatric disorder), severity of illness was no significant predictor of any of the GHQ- scale scores or the total score, nor for mothers, nor for fathers.

Present disease-related psychosocial limitations for parents

Table 3 shows the present parental limitations, related to the MSS. Results of one patient were not included in the table, since this patient can be regarded as an 'outlier' and the parents did not complete the GHQ. This patient became severely mentally and motorically retarded as a result of the MSS. Since the MSS, mother has to stay at home to take care for the child and is

Table 3. Present long-term limitations for parents of MSS-children

Disease related parental limitations (n)	no limitations (%)	moderate limitations (%)	severe limitations (%)
Possibility to make promotion at work (87)	no limitations	limitations for 1 parent	limitations for 2 parents
	98	2	0
If a parent is fulltime occupied with housekeeping, is MSS the reason why that person is not able to get a job? (36)	MSS not the reason	MSS reason next to others	MSS only reason
	92	8	0
Parental decision not to have further offspring (87)	no	no, but did ask help	yes
	92	1	7
Parental limitations concerning (86):	no		yes
- going on holiday	95		5
- going out	96		4
- membership of societies	99		1
- finding a babysitter/nanny	96		4
- leisure-time activities	99		1
- visiting family or friends	98		2
Needs for parental attention of MSS child, compared to siblings, as to (77):	less attention	equal attention	more attention
- sleeping (falling asleep, sleeping all night)	5	76	19
- eating/drinking	1	87	12
- bathing	3	90	7
- disciplining (complying to house rules)	16	67	17
- in traffic	8	81	11
- playing alone	8	83	9
- illness in general	6	77	17
- education/parenting in general	7	72	21
Is there present extra burden; financial, emotional or practical (87)	no	moderate	large
	75	16	9

therefore not able to have a paid job. These parents experience severe limitations in daily life being constantly occupied with the care of their child. They reported to experience extreme emotional, practical and financial burden as a result of the disease. The child's health status is very poor and his parents worry a lot about the future.

None of the parents in the sample mentioned the MSS as a sole reason for not having being able to make promotion at work or for the current absence of a paid job.

For 7% of the parents the MSS was reported to be the main cause for not having any further offspring.

Four to five percent of parents reported current limitations due to the MSS in leisure time activities such as going on holidays or going out.

When asked whether they have to pay more attention to the MSS-surviving child compared to his/her siblings, the vast majority of parents (ranging from 67% to 91%) reported that their MSS-surviving child needs equal attention compared to their siblings. Seventeen to twenty-one percent of the ex-patients require more parental attention as to going to bed, disciplining, illness in general and parenting in general.

Parents reported that in the first few years after the MSS the emotional burden was great, but than it gradually diminished. Still 9% of parents evaluated the current emotional burden due to the MSS as large. Parents reported that they often think about the traumatic event and they are troubled by thinking or reading/hearing about it. One father and 2 mothers were crying during the semi-structured interview.

During the interview 17% of parents reported that they still are extra alert and worried about illness in general of their child. They are afraid their child will become ill again and panic when the child has fever. Some parents reported they become more easily and to a larger extent concerned about illness in their child, other parents were also more concerned about illness regarding all their children.

Discussion

The main finding in the present study is that parents of children who survived MSS show lower levels of psychiatric symptoms than individuals in the general population, despite the fact that the illness' aftermath is still noticeable in a minority of parents 4 to 16 years after the child's illness. The vast majority of parents of children who survived MSS hardly experience any limitations at follow-up.

A possible explanation for our overall positive findings is that parents seem to worry less about 'futilities' in life, which may have resulted in the lower levels of psychiatric symptoms compared to the general population found in this study. Parents experience a great amount of stress at the time their children suddenly have this life-threatening disease. Uncertainties about a possible death, complications and long-term sequelae if their children survive, result in increasing or overwhelming stress and anxiety levels. If their children survive they stay on the PICU for a few days and then move to a general hospital for 1 or 2 weeks. Especially when there are minor sequelae, the family and the child go on with their daily activities. The stressful period is left behind them. In the psychological interviews done by the psychologist, parents reported they have learned to live with the event, it made them stronger and they have learned to appreciate life more. Although it seems paradoxical, parents reported to be strengthened by the MSS. Other explanations for our 'above average' favourable results are that social desirability, denial or overcompensation may have influenced the answers.

Our present favourable findings are in line with those of one study, who investigated the long-term psychological consequences in parents of a small (N= 50) and heterogeneous group of children with severe meningococcal disease (meningitis, septicaemia or both) (Ehrlich et al., 2005), whereas our sample consisted of only children with MSS.

Overall, mothers and fathers of children who survived MSS do not differ regarding their level of psychiatric symptoms. Our results are in contrast with a trend in the general population; where women show more GHQ-symptoms than men (Koeter & Ormel, 1992) and with results of one study; where mothers show higher prevalences of psychiatric symptoms at

3 and 6 months follow-up than fathers and fathers show higher prevalence of psychiatric symptoms at 12 months follow-up than mothers (Ehrlich et al., 2005).

In this study severity of illness is no significant predictor of mental health in parents at follow-up. Our results are in line with those of one study, who neither found a relationship between severity of illness and GHQ-scores at short term (Judge et al., 2002).

Overall, during interviews parents reported that in the first few years after the MSS the emotional burden was great, but then gradually on the burden and stress diminished. However, a minority of parents still experiences disease-specific limitations. Seven percent of the parents decided not to have any more children because they did not want to experience such a traumatic event as the MSS again. Parents report to be extra alert and concerned about illness in their child. They give their child more attention when the child is ill compared to siblings, while the child does not necessarily ask for more attention. About 20% of the parents report their MSS child needs more attention compared to the siblings as to sleeping at night and parenting and disciplining in general. Nine percent of the parents report that the present emotional burden of the MSS is still large. They often think about the traumatic event and they get emotional thinking or reading/hearing about it. This emotional burden and these current disease-specific limitations are not reflected in levels of psychiatric symptoms measured by the General Health Questionnaire however.

Strengths and limitations of the present study

A unique feature of this study is the homogeneous patient sample, consisting of only MSS patients, that has been investigated on the long-term (4-16 years). In contrast to most studies, both fathers and mothers participated in this study and standardized assessment procedures were used. Furthermore the response rate was high (74% for fathers, 84% for mothers). However, the GHQ measures a limited number of domains of psychiatric problems. This study has been done in one centre, and it is unknown to what extend idiosyncrasies of one centre has influenced our results.

Since the interview questions were designed specifically to address present parental limitations due to MSS no normative data for these questions are available. In the PICU it is not possible to find another critical illness with the same amounts of patients and age distribution, so we did not choose a small disease specific control group but large representative normative samples to compare our data with.

Implications

Overall, lower levels of psychiatric symptoms compared to reference groups were found in parents of children who survived MSS. The vast majority of parents experience hardly any disease-specific limitations due to the MSS. We need to remain alert for individual parents at risk of adjusting poorly, especially since a minority still reports present limitations and still experiences an extra emotional burden due to the MSS. Future research should focus on which variables are predictors for favourable versus unfavourable adjustment of parents.

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General Discussion

General Discussion

Present psychosocial functioning in children, adolescents and adults who survived septic shock

The main conclusion of the present study is that overall, children, adolescents and young adults, who survived Meningococcal Septic Shock (MSS) in childhood, are functioning well and are leading normal lives. Favourable outcomes on cognitive functioning, behavioural and emotional problems, including post-traumatic stress problems, and self-esteem were found.

This is remarkable since MSS has an immense biological and emotional impact on children and adolescents shortly after their admission to the PICU. A short-term study by our research group into outcome of MSS showed that parents reported behavioural and emotional problems in 13% of the children up to 2 years after MSS, although these problems were not measured with standardized instruments (Buysse et al., 2008). High risk for post-traumatic stress problems, emotional and hyperactivity symptoms and psychiatric disorders such as depressive, oppositional defiant and anxiety disorders was found in children shortly after MD or after a PICU admission in general (Judge et al., 2002; Rennick et al., 2002; Rees et al., 2004; Shears et al., 2005; Shears et al., 2007; Knoester et al., 2007). However, our study shows that overall, on the long-term, psychosocial outcomes are favourable.

Favourable psychosocial outcomes

MSS children and adolescents showed similar levels of behavioural and emotional problems, including post-traumatic stress problems compared to reference groups, according to both fathers and mothers, teachers and children themselves. MSS adults also reported similar levels of behavioural and emotional problems and in addition they did not differ from reference adults as to biographical characteristics.

Our research group also studied long-term Quality of Life (QoL) in the same patient sample and found favourable results on QoL as well; children and adults themselves reported more favourable scores on psychosocial functioning (general behaviour, family activities, role limitations due to emotional problems and psychosocial summary) compared to reference groups (Buysse et al., 2007).

Explanation. A possible explanation for our positive findings might be that survivors of MSS show resilience. MSS survivors may, paradoxically, be strengthened by their life-threatening illness. It might also be that MSS survivors are more appreciative of life. This 'positivism' was also seen in a study by Wallace et al. (2007); ex-patients spoke of positive changes to their selves and the way they now approach life, 1-7 years after meningococcal sepsis during adolescence (Wallace et al., 2007).

Previous studies. Several other studies investigated behavioural and emotional outcome long-term after MD, bacterial meningitis and PICU admission (Fellick et al., 2001; Bedford et al., 2001; Berg et al., 2002; Halket et al., 2003; Koomen et al., 2003; Knoester et al., 2007). Our favourable results as to behavioural and emotional problems are not in line with those studies. One study, using a heterogeneous sample of patients with MD, showed that at 10-year follow-up, parents and teachers reported significantly more cognitive and global problems and Attention Deficit Hyperactivity Disorder (ADHD) symptoms for ex-patients, but not more social problems (Fellick et al., 2001). Four studies showed that children who survived bacterial meningitis showed more behavioural and ADHD problems and a decreased health-related quality of life than reference children (Bedford et al., 2001; Berg et al., 2002; Halket et al., 2003; Koomen et al., 2003). A review showed that though a majority of PICU survivors (0-29 years old) showed a good quality of life, a minority still showed poor quality of life, 1-6 years after PICU admission (Knoester et al., 2007). These results are difficult to compare however, since different and mostly heterogeneous patient samples were used with different pathophysiologies.

Conclusion. Overall, it can be concluded that our homogeneous sample of children who survived MD showed favourable long-term outcomes as to behavioural and emotional problems.

Unfavourable psychosocial outcomes

Unfavourable psychosocial outcomes were found as to 1) cognitive functioning and 2) self-esteem.

1) Cognitive functioning

Overall, children, adolescents and young adults showed cognitive functioning in the normal range. However, impairments were found as to social and practical reasoning, visual-motor integration, attention and executive functioning in children and adolescents. In adults a non-significant trend towards a lower intellectual functioning was found.

Explanation. Visual-motor integration is located in the parietal cortical region and all other functions are located in the frontal cortical region. A possible explanation for our findings might be that cerebral hypoperfusion due to sepsis led to damage of the watershed area in the frontal lobe where a cerebri media and anterior meet as well as in the parietal lobe where a cerebri media and posterior meet. Another possible explanation for the frontal cognitive problems in MSS children is that the frontal lobe is not yet fully developed by the time MSS occurs (77% of the children had MSS before 4 years of age) and MSS impairs this development.

We have to be careful with these explanations, since no MRI data were available. In the future MRI scans and especially Diffusion Tensor Imaging, that shows the structural integrity of myelinated fibers, could specify the severity and location of frontal brain damage. Several studies focussed on brain (dys-) function in septic shock in adults and found that septic shock is associated with a spectrum of cerebral damage and dysfunction (Sharshar et al., 2005; Stochetti, 2005; Sharshar et al., 2007). However, it can be speculated that sepsis can have a different effect on the developing brain of a child or adolescent, in contrast to that on a fully developed brain of an adult person.

Previous studies as to cognitive functioning

Short-term studies: in only one short-term study neuropsychological assessment was performed in patients with MD 1 year after hospitalisation; neuropsychological impairment was found in 2 of 9 patients (Naess et al., 1994). 16 of in total 91 patients had EEG changes or borderline EEG abnormalities. Furthermore, sequelae were more common after serious septicaemia, regardless of the presence or absence of meningitis.

Long-term studies: in only one study cognitive functioning was investigated long-term (10 years) after MD; more cognitive problems (impairments in total, verbal and performal IQ and visual-motor integration) were found (Fellick et al., 2002). Several other long-term studies of cognitive outcome after bacterial meningitis also showed cognitive impairments (such as mental retardation) (Baraff et al., 1993; Taylor et al., 2000; Grimwood et al., 2000; Bedford et al., 2001; Koomen et al., 2003; Anderson et al., 2004). Cognitive impairments were also found in adult survivors of bacterial meningitis in childhood (Hugosson et al., 1997). In two studies postmeningitic children performed worse at school, went to special-needs school more often and repeated a grade more often (Taylor et al., 1998; Koomen et al., 2003). Three studies using different assessment points over time showed an overall cognitive impairment at initial assessment. At re-assessment 1 or 2-12 years later children remained at risk for cognitive impairment (Taylor et al., 1992; 2000, Grimwood et al., 1995; 2000; Anderson et al., 1997; 2004). No deterioration in cognitive functioning over time took place.

Conclusion: overall, it can be concluded that MSS children, adolescents and adults showed long-term cognitive functioning in the normal range. However impairments were found as to social and practical understanding, visual-motor integration, executive functioning and attention. In the future MRI scans could specify the severity and location of frontal brain damage.

2) Self-esteem

MSS children obtained scores on self-esteem comparable to those of reference children. However, MSS adolescents reported lower self-esteem than reference adolescents. Self-esteem was also related to the presence and evaluation of scars.

Explanation. In the present study MSS adolescents showed less favourable outcomes than MSS children. This is in line with trends in the general population: a dramatic decrease in self-esteem during the transition from childhood to adolescence is often reported (Major et al., 1999; Robins et al., 2002). Adolescence is a stressful developmental stage and having experienced a life-threatening illness as MSS may increase feelings of vulnerability and thus on the long-term negatively influence self-esteem.

In addition, MSS adolescents with scars reported lower global self-worth than MSS adolescents without scars. MSS adolescents may perceive the scars as symbolic constant reminders of having experienced a life-threatening illness, which might result in feelings of vulnerability. The worse MSS adolescents evaluated their scars, the worse their outcomes on close friendship, but the better their outcomes on social acceptance and behavioural conduct. The discounting hypothesis might explain this: MSS adolescents with worse scarring might devaluate physical appearance as less important (the domain of self-esteem in which they fail), and might perceive social acceptance and behaviour as more important. Fear of rejection might interfere with self-esteem in the particular 'intimacy' domain (close friendship).

Previous studies. The possible decreased value MSS adolescents may attribute to appearance has also been described in a qualitative study into a small sample of adolescents who survived meningococcal septicaemia, 1-7 years after the illness (Wallace et al., 2007). Wallace et al. (2007) concluded that adolescents seemed to have accepted their new appearance and to have adapted satisfactorily. The adolescents incorporated their new appearance into their identity and made a shift from upward to downward social comparisons. However, Wallace et al. (2007) did not measure self-esteem with standardized instruments.

Several other studies into outcome for burn victims with scars also reported positive findings; they all found higher or similar self-esteem, psychosocial adjustment or competence short and long-term after burns (6 months to 12 years) (Moore et al., 1996; LeDoux et al., 1996; Blakeney et al., 1998; Baker et al., 2007; Pope et al., 2007). One study showed higher self-esteem as to social acceptance and job competence, and lower self-esteem on the domains of athletic competence and physical appearance (Robert et al., 1999). Liber et al. (in press) referred to the concepts of 'Post-traumatic growth' and 'resilience' to explain long-term positive outcomes as to problem behaviour, depressive symptoms, personality traits and coping styles in adolescents 10 years after they were burned.

Conclusion: overall, it can be concluded that MSS children show similar self-esteem compared to reference children whereas MSS adolescents, especially those with skin scarring, show lower self-esteem.

Psychosocial functioning in parents of children who survived septic shock

Overall, MSS parents reported to have a better mental health than a normative reference group. Nevertheless, a minority of MSS parents still experiences disease-related psychosocial limitations, including the decision not to have more children, the elevated need for more parental attention in the MSS child and the current emotional burden because of the MSS.

Explanation. Although it seems paradoxical, parents seem to have been strengthened by the experience of MSS in their child. They also told during the interviews that they have learned to live with the event and learned to appreciate life more. The acute phase and the first few years were difficult. Having a child with MSS and the admission at a PICU is perceived as a major emotional stressor (Haines, 2005). In a study by our research group 17% of 47 mothers had anxiety or depression requiring professional help within 2 years after the child had survived MSS (Buysse et al., 2008).

Previous studies into psychosocial functioning in parents

Short-term studies: studies into short-term psychological outcome of MD or general PICU admission reported similar results (Colville & Gracey, 2006; Judge et al., 2002; Rees et al., 2004; Ballufi et al., 2004; Shears et al., 2005; Ehrlich et al., 2005; Shudy et al., 2007). High risk for negative psychological outcome was consistently found, especially high risk for PTSD. Several studies showed that parental stress levels were higher when parents experienced an unplanned PICU admission, when critically ill children were diagnosed with an illness/injury that would have a chronic component and when children were clinically unstable (Eberly et al., 1985; Tomlinson et al., 1995; Board & Ryan-Wenger, 2003).

Long-term studies: Our present favourable results as to parental mental health are in line with those of another long-term study by our research group of the same parent population; parents obtained better scores on psychosocial domains of HRQoL (social functioning, mental health and role functioning emotional) (Buysse et al., 2007). Previously, only one study focussed on long-term psychological outcome after MD in parents (Ehrlich et al., 2005). This study also showed favourable results; psychological distress levels were comparable to those of a normative reference group (Ehrlich et al., 2005). Even two short-term studies described a trend towards decreasing stress and anxiety levels over time (Shudy et al., 2006; Board & Ryan-Wenger, 2002).

In a meta-analysis of 66 studies that used Horowitz's Impact of Event Scale (IES) to examine the psychological impact of a major life event (illness and injury, natural and technological disaster, bereavement and loss, violence, sexual abuse and war exposure) on adults on the long-term also favourable outcomes were found (Sundin & Horowitz, 2003). A number of studies presented longitudinal data on the IES and a general trend indicated that there was a decrease in stress reactions over time. Intrusive and avoidant reactions reported by trauma victims tended to decrease linearly over time (up to 3 years or more) after the trauma (Sundin & Horowitz, 2003).

Explanatory models: Mc Cubbin's Family Adjustment and Adaptation Response model (1996) and Mc Cubbin's resiliency model of Family Stress, Adjustment and Adaptation (2000) are often used to interpret findings of reduced parental stress over time (after trauma). Both theoretical models state that the ability of a family to adapt to stress depends on the relative balance between the stressor and stains experienced by the family on the one hand and the resources and coping strengths on the other hand. A crisis places an immense burden on the family, but according to this model, families will restore the balance and adapt to the situation when stress decreases. The 'meanings' the family describes to an experience or crisis and their own resources for coping are critical factors in achieving this balance.

The response shift model can be used to explain our positive results as to *better* mental health in MSS parents (Moons, 2004). This model was developed in reaction to the amount of counterintuitive results showing that patients who experience a life-threatening disease can report a good quality of life. According to this model the internal standards and values of these patients may be changed because of this experience. It is possible that parents of children who survived MSS also re-evaluate goals and adopt new values and meanings to their sense of life, because they have almost lost their child. They may not worry about futilities and value life more. Parents also reported this during the semi-structured interviews. Grootenhuis et al. (1997) also described this phenomenon in parents of children with cancer.

Furthermore, Calhoun & Tedeschi (1998) stated that positive changes may occur after negative life events (such as major loss or trauma). They described those changes as "post-traumatic growth".

Conclusion. Overall, previous studies showed that on short-term MSS parents experience elevated stress levels. The present study showed that on the long-term, MSS parents showed favourable, even better than 'normal' outcomes as to mental health.

Role of gender, age at time of illness, age at time of follow-up, severity of illness and other medical variables on psychosocial functioning of MSS patients and their parents

Gender

Results indicate that MSS boys show more behavioural and emotional problems (somatic complaints and total problems) and lower self-esteem (as to behavioural conduct) than MSS girls, while in the reference population girls show more of these problems than boys (group x gender interaction-effects). However, these results became non-significant after Bonferroni correction for multiple testing.

When comparing MSS boys with reference boys, and MSS girls with reference girls, it seems that more behavioural and emotional problems and a lower self-esteem were found for MSS boys and to a much lesser extent for MSS girls. Within the adult sample male gender was a predictor for internalising as well as for externalising problems, whereas male gender is only associated with more externalising problems in the general population. Taylor et al. (1990), Berg et al. (2002) and Koomen et al. (2003) also reported in three long-term studies that boys were more at risk for behavioural problems 6-14 years after bacterial meningitis .

As to cognitive functioning of MSS children, adolescents and adults and mental health of parents, overall, no differences between boys and girls were found.

Conclusion as to gender-effects. Overall, our results indicate that male gender was a risk factor for behavioural and emotional problems and lower self-esteem in the MSS child-, adolescent and adult sample.

Age at time of illness

Overall, age at time of illness was not associated with self-esteem and parental mental health. Furthermore, overall, it was neither associated with cognitive problems in the child-, adolescent- and adult sample. This is in contrast with two theories about early brain damage: the vulnerability and the plasticity theory, with brain damage at an early age causing respectively more or less deficits later on. The majority of studies into bacterial meningitis and Traumatic Brain Injury (TBI) favour the vulnerability theory, finding more cognitive problems on the long-term (7-12 years) when children were younger at time of illness or injury (Grimwood et al., 1996; Taylor et al., 1997; Anderson et al., 1997; Taylor et al., 2000; Anderson et al., 2004, 2005). Taylor et al. (1997) described in a review on TBI that age-related effects were most clearly evident when comparing children younger versus older than 7 years of age. A possible explanation for the lack of finding an age effect in our child and adolescent sample might be that 96% of the MSS patients were younger than 7 years at time of illness.

As to behavioural and emotional problems, younger age at time of illness was associated with more behavioural and emotional problems, in the child-, adolescent- and adult sample. A possible explanation for these findings in both samples is that there is no rooming in at the PICU and especially for preschoolers being separated from their parents is more traumatic than for older children. Stuber & Shemesh (2006) describe that younger children are more likely than older children to find separation from friends and family to be a major traumatic event. However, we have to keep in mind that overall, children, adolescents and adults obtained scores for behavioural and emotional problems that were within the normal range.

Conclusion as to age at time of illness. Overall, age at time of illness is not related to cognitive functioning and self-esteem in MSS children, adolescents and adults, neither to mental health in their parents. Within the MSS sample, younger age at time of illness is associated with more behavioural and emotional problems.

Age at time of follow-up

Overall, it seems that MSS adolescents are at risk for cognitive impairments, behavioural and emotional problems and lower self-esteem long-term after they have survived MSS, whereas this is less the case for MSS children. Age at time of follow-up of the MSS children and adolescents did not show a relationship with parental mental health.

In the child and adolescent sample, older age at time of follow-up was a significant predictor for worse cognitive functioning on the long-term. In the adult sample however, age at time of follow-up was no significant predictor for cognitive functioning. We gave as possible explanation for the effect of age in the child- and adolescent sample the 'growing into deficits' phenomenon: 'early brain damage may result in a cumulative effect on ongoing development, and increasing deficits may emerge through childhood as more functions are expected to mature and will need to be subsumed within the undamaged tissues'. Two studies into childhood brain insults, including Traumatic Brain Injury (TBI), and into bacterial meningitis specifically, also found an 'emergence or worsening of cognitive deficits with age' (Taylor et al., 1997, 2000). They argued that this was caused by damage to brain regions that mediate later-developing functions and deficits in the ability to learn efficiently and accumulate knowledge. We did not find an effect of age at time of follow-up in the adult sample however. Two other studies into bacterial meningitis did not find a deterioration in cognitive skills at different time points (Grimwood et al., 1995, 2000; Anderson et al., 1997, 2004).

As to behavioural and emotional problems, when comparing directly younger and older MSS children, overall no differences between them were found. When comparing MSS children and MSS adolescents with same-aged reference persons, only one significant effect appeared: more MSS adolescents (12-17 years old) obtained total problem scores in the deviant range. In the adult sample (19-31 years old), younger age at time of follow-up was a significant predictor for behavioural and emotional problems (Externalising, Rule-Breaking Behaviour). It is difficult to draw firm conclusions but findings seem to indicate that MSS adolescents at the end of adolescence are the most at risk for behavioural and emotional problems.

Though age at time of follow-up was not related to long-term self-esteem, MSS adolescents reported lower self-esteem compared to same-aged reference adolescents, while MSS children reported higher self-esteem than same-aged reference children.

Conclusion as to age at time of follow-up. Overall, it can be concluded that MSS adolescents are more at risk for cognitive-, behavioural and emotional problems and a lower self-esteem than MSS children.

Severity of illness

MSS children, adolescents and adults. Overall, it can be concluded that severity of illness, measured by the PRISM score, was not related to long-term psychosocial outcome on cognitive functioning, behavioural and emotional problems, including post-traumatic stress problems and self-esteem, neither in the child-, nor in the adolescent or adult sample. This conclusion is in contrast with our expectation to find more long-term psychosocial problems with more severe illness.

Our results are also in contrast with those of studies focussing on short-term outcome (3-12 months) after MD or PICU admission. In these studies severity of illness was related to psychiatric symptoms in children with MD (Rennick et al., 2002, Shears et al., 2005, 2007).

Parents. In addition, severity of illness of the MSS patient was not related to long-term mental health in parents. In the majority of studies into short-term psychological outcome in mothers or in both parents similar results were found; severity of illness was not related to Acute Stress Disorder (ASD), PTSD symptoms and psychological distress in parents of PICU children (Judge et al., 2002; Colville & Gracey, 2006; Ballufi et al., 2004).

A possible explanation for finding no relationship between severity of illness and long-term parental mental health in the present study might be that parental perceptions of severity of illness may show discrepancies from more objective measures of severity, calculated by paediatricians at time of illness (for example PRISM). Parents' perception of severity of illness may correspond closer to their own experience and feelings and emotions. Probably a relationship between severity of illness and parental mental health would have been found when parents' perception of severity of illness was used.

Different illnesses. A previous study used children with several different illnesses, including children with MD (Grootenhuis et al., 2007). This study reported that MD children were not different from healthy controls, but children with cancer, coeliac disease, CHD and asthma had significant lower HRQoL than healthy controls (all in different domains). Unfortunately it is not clear in the description of the study which follow-up intervals for different patient samples were used. Two other studies showed a trend towards less anxiety and depression in sepsis patients compared to patients with other critical illnesses without sepsis and compared with patients with trauma (respectively 6 months, and 2 years after ICU) (Granja et al., 2004; Jagodic et al., 2006). These patients became ill at an adult age.

The above studies into MD patients and sepsis patients showed favourable outcomes, as in our study. Moreover, these studies also seem to indicate that illnesses with different pathophysiologies and different severities have a disease-specific impact on psychosocial outcomes. It is difficult to draw firm conclusions, because these studies used patient samples with different basic characteristics (for example age or length of stay), different follow-up intervals and different outcomes.

Conclusion as to severity of illness. Severity of illness, measured by the PRISM score, was not related to psychosocial functioning in children, adolescents and adults who survived MSS, neither to mental health in their parents.

Other medical variables as possible predictors for cognitive functioning

None of the other medical variables, including presence of convulsions, corticosteroids administration, PRISM, DIC, VAS, length of stay and serum glucose level were significant predictors per se for cognitive functioning. Only combinations of medical variables (highest serum glucose level, serum glucose level at time of admission, VAS and length of stay) predicted a worse outcome on three domains of neuropsychological functioning. Future research should be done to investigate more in detail the relation between medical variables, especially hyperglycemia and hypoglycaemia, in MSS patients, and long-term cognitive outcome.

Strengths and limitations

Psychosocial functioning after MSS in children, adolescents and adults, and in their parents, has not been investigated before, neither on short-term, nor on the long-term. A unique feature of this study is the homogeneous patient sample of MSS survivors. Standardized assessment procedures and semi-structured interviews were used. Overall the response rate was high. A multi-informant approach was used to assess behavioural and emotional problems; mothers, fathers, teachers and children themselves completed the questionnaires. Large representative reference groups were used to compare our data with. In the PICU it is not possible to find another critical illness with the same amounts of patients and age distribution, so we did not choose a small disease specific comparison group. Furthermore a small comparison group can be biased.

This cross-sectional study has been done in one center, and therefore generalizability of our findings can be questioned. This study was not longitudinal, therefore caution should be made in drawing conclusions about functioning at different ages and over time. Due to small numbers of patients without meningitis in the sample as to cognitive functioning we were not able to perform statistical analyses in this subsample. Furthermore no information of neuro-imaging at time of illness or in the period following MSS was available. It is unknown to what extend differences between responders and non-responders (such as age, gender and severity of illness) may have influenced our findings. Unfortunately no information as to premorbid functioning was available.

Future research

Future research should be done to replicate our findings as to cognitive functioning. Neuro-imaging (MRI) should be included to detect and locate areas in the brain where damage may have occurred.

Premorbid characteristics were found to be of predictive value for PTSD symptoms 3 months after MD (Shears et al., 2005; Shears et al., 2007), but unfortunately no information as to premorbid characteristics was available in the present study. Future research should also involve premorbid characteristics.

When investigating the relationship between scarring and self-esteem, consideration should be given to the amount of scarring, for example with the Total Body Surface Area (TBSA), which is used in many studies into outcome after burning accidents (Blakeney et al., 1998; Moore et al., 1996; Robert et al., 1999; Baker et al., 2007; LeDoux et al., 1996).

Furthermore it has to be considered that although parents reported a similar or even better mental health, a minority still experiences disease-related limitations. A disease-specific questionnaire should be developed and used in future research to explore these limitations.

Clinical implications

This thesis provides an overview of the long-term consequences of having survived MSS in childhood. This information can be used to guide adequate counselling. The present study provides several clinical implications:

- From literature it can be concluded that on short-term an elevated risk for PTSD was found in children with critical illnesses such as MD, bacterial meningitis and PICU admissions, as well as in their parents. Buysse et al. (2008) found that parents of children who survived MSS reported psychological problems regarding themselves and their children up to 2 years after PICU admission. In the present study parents often indicated that they would have wanted psychosocial help shortly after their child survived MSS. We advice that at short-term a psychological screening should take place in MSS survivors and/or their parents, for example 3 months after PICU discharge. In this psychological screening the focus should be on behavioural and emotional problems in children (for example using the CBCL) and PTSD symptoms in parents. If indicated, adequate interventions or treatment should then be offered.
- Although in the present study overall favourable long-term psychosocial outcomes were found for MSS children, adolescents and adults, slight impairments were found on the domain of neuropsychological functioning and self-esteem. We advice to provide structured information about long-term outcomes, especially as to impairments on neuropsychological functioning and self-esteem to parents and teachers, to make them alert for recognizing these deficits. Adequate professional help for these impairments can then be sought (for example psychological counselling, plastic surgery, remedial teaching, screening for cognitive impairments after MSS in a rehabilitation centre for children with acquired brain injuries).

References

References

Aarsen F.K., Paquier, P.F., Reddingius, R.E., Streng, I.C., Arts, W.F., Evera-Preesman, M. et al., (2005). Functional outcome after low-grade astrocytoma treatment in childhood. *Cancer*, 106, 396-402.

Aasland, A., & Diseth, T.H. (1999). Can the Harter Self-Perception Profile for Adolescents (SPPA) be used as an indicator of psychological outcome in adolescents with chronic physical disorders? *European Child & Adolescent Psychiatry*, 8, 78-85.

Achenbach, T.M., & Rescorla, L.A. (2001). *Manual for the ASEBA school-age forms & profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth & Families.

Achenbach, T.M. & Rescorla, L.A. (2003). *Manual for the ASEBA adult forms & profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2003.

Achenbach, T.M., & Rescorla, L.A. (2007). *Multicultural Supplement to the Manual for the ASEBA School-Age Forms & Profiles.* Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Anderson, V., Bond, L., Catroppa, C., Grimwood, K., Keir, E., & Nolan, T. (1997). Childhood bacterial meningitis: impact of age at illness and acute medical complications on long-term outcome. *Journal of the International Neuropsychological Society*, 3(2), 147-158.

Anderson, V., Anderson, P., Grimwood, K., & Nolan, T. (2004). Cognitive and executive function 12 years after childhood bacterial meningitis: effect of acute neurologic complications and age of onset. *Journal of Pediatric Psychology*, 29(2), 67-81.

Anderson, V., Catroppa, C., Morse, S., Haritou, F., & Rosenfeld, J. (2005). Functional plasticity or vulnerability after early brain injury? *Pediatrics*, 116(6), 1374-1382.

Andrews, T.K., Rose, F.D., & Johnson, D.A. (1998). Social and behavioral effects of traumatic brain injury in children. *Brain Injury*, 12, 133-138.

Bache, C.E., & Torode, I.P. (2006). Orthopedic sequelae of meningococcal septicaemia. *Journal of Pediatric Orthopedics*, 26, 135-139.

Baines, P.B., & Hart, C.A. (2003). Severe meningococcal disease in childhood. *British Journal of Anaesthesia, 90* (1), 72-83.

Baker, C.P., Russell, W.J., Meyer, W., & Blakeney, P. (2007). Physical and psychologic rehabilitation outcomes for young adults burned as children. *Archives of Physical Medicine and Rehabilitation*, 88(2), S57-S64.

Balluffi, A., Kassam-Adams, N., Kazak, A., Tucker, M., Dominguez, T., & Helfaer, M. (2004). Traumatic stress in parents of children admitted to the pediatric intensive care unit. *Pediatric Critical Care Medicine*, 5(6), 547-553.

Baraff, L.J., Lee, S.I., & Schriger, D.L. (1993). Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatric Infectious Disease Journal*, 1993, 12(5): 389-394.

Bedford, H., Louvois de, J., Halket, S., Peckham, C., Hurley, R., & Harvey, D. (2001). Meningitis in infancy in England and Wales: follow-up at age 5 years. *BMJ* 2001; 323: 1-5.

Belek, I. (2000). Social class, income, education, area of residence and psychological distress: does social class have an independent effect on psychological distress in Antalya, Turkey? *Social Psychiatry and Psychiatric Epidemiology, 35*, 94-101.

Beery K. (1997). *Developmental Test of Visual-Motor Integration, Fourth Edition*. Parsippany, NJ: Modern Curriculum Press.

Belthur, M.V., Bradish, C.F., & Gibbons, P.J. (2005). Late orthopedic sequelae following meningococcal septicaemia. A multicentre study. *The Journal of Bone and Joint Surgery (American)*, 87, 236-240.

Berg, S., Trollfors, B., Hugosson, S., Fernell, E., & Svensson, E. (2002). Long-term follow-up of children with bacterial meningitis with emphasis on behavioural characteristics. *European Journal of Pediatrics*, 161, 330-336.

Birndorf, S.D.O., Ryan, S., Auinger, P., & Aten, M. (2005). High self-esteem among adolescents: Longitudinal trends, sex differences, and protective factors. *Journal of Adolescent Health*, 35, 194-201.

Blakeney, P., Meyer, W., Robert, R., Desai, M., Wolf, S., & Herndon, D. (1998). Long-term psychosocial adaptation of children who survived burns involving 80 % or greater total body surface area. *The Journal of Trauma*, 44(4), 625-634.

Board, R., & Ryan-Wenger, N. (2002). Long-term effects of pediatric intensive care unit hospitalization on families with young children. *Heart & Lung*, 31 (1), 53-66.

Board, R., & Ryan-Wenger, N. (2003). Stressors and stress symptoms of mothers with children in the PICU. *Journal of Pediatric Nursing*, 18(3), 195-202.

Boeckaerts, M., & Röder, I. (1999). Stress, coping, and adjustment in children with a chronic disease: a review of the literature. *Disability and Rehabilitation* , 21, 311-337.

Bos, A.E.R., Muris, P., Mulkens, S., & Schaalma, H.P. (2006). Changing self-esteem in children and adolescents: a roadmap for future interventions. *Netherlands Journal of Psychology*, 62, 26-33.

Buysse, C.M.P., Raat, H., Hazelzet, J.A., Vermunt, L.C.A.C., Utens, E.M.W.J., Hop, W.C.J., et al. (2007). Long-term health-related quality of life in survivors of meningococcal septic shock in childhood and their parents. *Quality of Life Research*, 16, 1567-1576.

Buysse, C.M.P., Raat, H., Hazelzet, J.A., Hop, W.C.J., Maliepaard, M., & Joosten, K.F.M. (2008). Surviving meningococcal septic shock: health consequences and quality of life in children and their parents up to 2 years after pediatric intensive care unit discharge. *Critical Care Medicine*, 36(2), 596-602.

Caffo, E., & Belaise, C. (2003). Psychological aspects of traumatic injury in children and adolescents. *Child and Adolescent Psychiatric Clinics of North America, 12*, 493-535.

CBS, *Statline Databank, Central Bureau of Statistics* http://www.cbs.nl/nl-NL/default.html, *Accessed 1 January 2007*

Cohen, J.B. (1988). *Statistical Power Analysis for the Behavioural Sciences* (2nd ed.). Hillsdale: Lawrence Erlbaum Associates.

Colville, G.A., & Gracey, D. (2006). Mothers' recollections of the Paediatric Intensive Care Unit: associations with psychopathology and views on follow-up. *Intensive and Critical Care Nursing*, 22, 49-55.

Cooper, C., Wheeler, D.M., Woolfenden, S.R., Boss, T., & Piper, S. (2006). Specialist home-based nursing services for children with acute and chronic illnesses (Review). *Cochrane database of systematic reviews*.

Crocker, J., & Park, L.E. (2003). Seeling self-esteem: construction, maintenance, and protection of self-worth. In Bos, A.E.R., Muris, P., Mulkens, S., & Schaalma, H.P. (2006). Changing self-esteem in children and adolescents: a roadmap for future interventions. *Netherlands Journal of Psychology*, 62, 26-33.

Draaijers, L.J., Tempelman, F.R., Botman, Y.A., Tuinebreijer, W.E., Middelkoop, E., Kreis, R.W., et al. (2004). The patient and observer scar assessment scale: a reliable and feasible tool for scar evaluation. *Plastic and Reconstructive Surgery*, 113, 1960-1967.

Dubois, D.L., Felner, R.D., Brand, S., Phillips, R.S.C., & Lease, A.M. (1996). Early adolescent self-esteem: a developmental-ecological framework and assessment strategy. Journal of Research on Adolescence, 6, 543-379. In Dubois, D.L., Tevendale, H.D., Burk-Braxton, C., Swenso, L.P., & Hardesly, J.L. (2000). Self-system influences during early adolescence: investigation of an integrative model. *Journal of Early Adolescence*, 20, 12-43.

Dubois, D.L., Tevendale, H.D., Burk-Braxton, C., Swenso, L.P., & Hardesly, J.L. (2000). Self-system influences during early adolescence: investigation of an integrative model. *Journal of Early Adolescence*, 20, 12-43.

Dubois, D.L., & Hirsch, B.J. (2000). Self-esteem in early adolescence: from stock character to marquee attraction. *Journal of Early Adolescence*, 20, 5-11.

Dusek, J.B. (2000). Commentary on the special issue: the maturing of self-esteem research with early adolescents. *Journal of Early Adolescence*, 20, 231-240.

Eberly, G., Miles, M.S., Carter, M.C., Hennessey, J., & Riddle, I. (1985). Parental stress after the unexpected admission of a child to the intensive care unit. Critical Care Quarterly, 8, 58-65.

Ehrlich, T.E., Von Rosenstiel, I.A., Grootenhuis, M.A., Gerrits, A.I., & Bos, A.P. (2005). Long-termpsychological distress in parents of child survivors of severe meningococcal disease. *Paediatric Rehabilitation, 8*(3), 220-224.

Eddleston, J.M., White, P., & Guthrie, E. (2000). Survival, morbidity, and quality of life after discharge from intensive care. *Critical Care Medicine*, 28 (7), 2293-2299.

Erickson, L., & De Wals, P. (1998). Complications and sequelae of meningococcal disease in Quebec, Canada, 1990-1994. *Clinical Infectious Diseases* , 26, 1159-1164.

Erickson, L.J., De Wals, P., McMahon J., & Heim, S. (2001). Complications of meningococcal disease in college students. *Clininal Infectious Diseases*, 33, 737-739.

Erickson, S.E., & Martin, G.S. (2008). Effect of sepsis therapies on health-related quality of life. *Critical Care*, 12(1), 109.

Fellick, J.M., Sills, J.A., Marzouk, O., Hart, C.A., Cooke, R.W.I., & Thomson, A.P.J. (2001). Neurodevelopmental outcome in meningococcal disease: a case-control study. *Archives of Disease in Childhood, 85*, 6-11.

Fellick, J.M., & Thomson, A.P.J. (2002). Long-term outcomes of childhood meningitis. Hospital Medicine, 63(5), 274-277.

Goldberg, D.P. & Hillier, V.F. (1979). A scaled version of the General Health Questionnaire. *Psychological Medicine, 24,* 18-26.

Goldberg, D.P. & Williams, P. (1988). *A users guide to the General Health Questionnaire*. Windsor. Nfer Nelson.

Granja, C., Dias, G., Costa-Pereira, A., & Sarmento, A. (2004). Quality of life of survivors from severe sepsis and septic shock may be similar to that of other who survive critical illness. *Critical Care*, 8, R91-R98.

Griffiths, J., Fortune, G., Barber, V., & Young, J.D. (2007). The prevalence of post-traumatic stress disorder in survivors of ICU treatment: a systematic review. *Intensive Care Med*, 33, 1506-1518.

Grimwood, K., Anderson, V.A., Bond, L., Catroppa, C., Hore, R.L., Keir, E.H., et al. (1995). Adverse outcomes of bacterial meningitis in school-age survivors. *Pediatrics*, 95(5), 646-656.

Grimwood, K., Nolan, T.M., Bond, L., Anderson, V.A., Catroppa, C., & Keir, E.H. (1996). Risk factors for adverse outcomes of bacterial meningitis. *Journal of Paediatrics and Child Health* , 32, 457-462.

Grimwood, K., Anderson, P., Anderson, V., Tan, L., & Nolan, T. (2000). Twelve year outcomes following bacterial meningitis: further evidence for persisting effects. *Archives of Disease in Childhood*, 83, 111-116.

Grootenhuis, M.A., Koopman, H.M., Verrips, E.G.H., Vogels, A.G.C., & Last, B.F. (2007). Health-related qualtiy of life problems in children aged 8-11 years with a chronic disease. Developmental Rehabilitation, 10(1), 27-33.

Gunther, M.L., Jackson, J.C., & Ely, W.E. (2007). The cognitive consequences of critical illness: practical recommendations for screening and assessment. *Critical Care Clinics*, 23, 491-506.

Haines, C. (2005). Parents' experiences of living through their child's suffering from and surviving severe meningococcal disease. *Nursing in Critical Care, 10* (2), 78-89.

Halket, S., Louvois de, J., Holt, D.E., & Harvey, D. (2003). Long-term follow-up after meningitis in infancy: behaviour of teenagers. *Archives of Disease in Childhood*, 88, 395-398.

Harter, S. (1988). *Manual for the Self-Perception Profile for Adolescents*. Denver, CO: University of Denver.

Harter, S. (1985). *Manual for the Self-Perception Profile for Children*. Denver: University of Denver.

Harter, S. (1993). Causes and consequences of low self-esteem in children and adolescents. In: Baumeister RF, ed. *Self-Esteem: the Puzzle of Low Self-Regard*. New York: Plenum Press.

Harter, S. (1999). *The construction of the self. A developmental perspective*. New York: The Guilford Press.

Hazelzet, J.A. (2005). Diagnosing meningococcemia as a cause of sepsis. *Pediatric Critical Care Medicine*, 6, 50-54.

Heyland, D.K., Hopman, W., Coo, H., Tranmer, J., & McColl, M.A. (2000). Long-term health-related quality of life in survivors of sepsis. Short Form 36: A valid and reliable measure of health-related quality of life. *Critical Care Medicine*, 28 (11), 3599-3605

Hopkins, R.O., Ely, W.E., & Jackson, J.C. (2007). The role of future longitudinal studie in ICU survivors: understanding determinants and pathophysiology of brain dysfunction. *Current Opinion in Critical Care*, 13, 497-502.

Hugosson, S., Carlsson, E., Borg, E., Brorson, L-O., Langeroth, G., & Olcen, P. (1997). Audiovestibular and neuropsychological outcome of adults who have recovered from childhood bacterial meningitis. *International Journal of Pediatric Otorhinolaryngology*, 42, 149-167.

Ireys, H.T., Gross, S.S., Werthamer-Larson, L.A., & Kolodner, K.B. (1994). Self-esteem of young adults with chronic health conditions: Appraising the effects of perceived impact. *Journal of Developmental and Behavioral Pediatrics,* 15, 409-415.

Jagodic, H.K., Jagodic, K., & Podbregar, M. (2006). Long-term outcome and quality of life of patients treated in surgical intensive care: a comparison between sepsis and trauma. *Critical Care*, 10, R134.

Joosten, K.F.M., De Kleijn, E.D., Westererp, M., De Hoog, M., Eijck, F.C.V., Hop, W.C.J., et al. (2000). Endocrine and metabolic responses in children with meningococcal sepsis: striking differences between survivors and nonsurvivors. *The Journal of Clinical Endocrinology & Metabolism, 85* (10), 3746-3753.

Judge, D., Nadel, S., Vergnaud, S., & Garralda, M.E. (2002). Psychiatric adjustment following meningococcal disease treated on a PICU. *Journal of Intensive Care Medicine*, *28*, 648-650.

Kim-Cohen, J., Moffitt, T.E., Caspi, A., & Taylor, A. (2004). Genetic and environmental processes in young children's resilience and vulnerability to socio-economic deprivation. *Child Development, 75* (3), 651-668.

Kling, K.C., Hyde, J.S., Showers, C.J., & Buswell, B.N. (1999). Gender differences in self-esteem: a meta-analysis. *Psychological Bulletin*, 125, 470-500.

Knoester, H., Grootenhuis, M.A., & Bos, A.P. (2007). Outcome of paediatric intensive care survivors. *European Journal of pediatrics*, 166, 1119-1128.

Koeter, M.W.J., & Ormel, J. (1992). *General Health Questionnaire. Dutch Version. Manual.* Lisse: Swets & Zeitlinger.

Koomen, I. (2003). *Prognosis of bacterial meningitis in childhood*. Doctoral dissertation, Labor Grafimedia BV, Utrecht.

Koomen, I., Grobbee, D.E., Jennekens-Schinkel, A., Roord, J.J., & Furth van, A.M. (2003). Parental perception of educational, behavioural and general health problems in school-age survivors of bacterial meningitis. *Acta Paediatrica*, 92, 177-185.

Koomen, I., Furth van, A.M., Kraak, M.A.C., Grobbee, D.E., Roord, J.J., & Schennekens-Schinkel, A. (2004). Neuropsychology of academic and behavioural limitations in school-age survivors of bacterial meningitis. *Developmental Medicine and Child Neurology*, 46, 724-732.

Koomen, I., Grobbee, D.E., Roord, J.J., Jennekens-Schinkel, A., Lei van der, H.D.W., Kraak, M.A.C., et al. (2004). Prediction of academic and behavioural limitations in school-age survivors of bacterial meningitis. *Acta Paediatrica*, 93, 1378-1385.

Kort, W., Schittekatte, M., Compaan, E.L., Bosmans, M., Bleichrodt, N., Vermeir, G., et al., (2002). *WISC-III. Handleiding. Nederlandse bewerking.* London: The Psychological Corporation.

Leary, M.R., & Baumeister, R.F. (2000).The nature and function of self-esteem: Sociometer Theory. In Bos, A.E.R., Muris, P., Mulkens, S., & Schaalma, H.P. (2006). Changing self-esteem in children and adolescents: a roadmap for future interventions. *Netherlands Journal of Psychology*, 62, 26-33.

Leary MR, MacDonald G. Individual differences in self-esteem: a review and theoretical integration. In Bos, A.E.R., Muris, P., Mulkens, S., & Schaalma, H.P. (2006). Changing self-esteem in children and adolescents: a roadmap for future interventions. *Netherlands Journal of Psychology*, 62, 26-33.

Lezak, M.D. ed. (2004). *Neuropsychological assessment. 4th Edition*. New York: Oxford University Press.

LeDoux, J.M., Meyer, W.J., Blakeney, P., & Herndorn, D. (1996). Positive Self-Regard as a Coping Mechanism for Pediatric Burn Survivors. *Journal of Burn Care and Rehabilitation* , 17, 472-476.

Liber, J.M., Faber, A.W., Treffers, A., & Van Loey, N.E.E. (in press). Coping style, personality and adolescent adjustment 10 years post-burn. *Burns* (2008).

Luteijn, F., & Barolds, D.P.H. (2004). *Groninger Intelligentie Test 2: handleiding*. Harcourt Assessment BV, Amsterdam.

Maat, M., Buysse, C.M.P., Emonts, M., Spanjaard, L., Joosten, K.F.M., Groot, R.D., et al. (2007). Improved survival of children with sepsis and purpura: effects of age, gender and era. *Critical Care*, 11 (5), R112.

Manly, T. ed. (1999). *The Test for Everyday Attention for Children (TEA-Ch).* Thames Valley Test Company: Bury St. Edmunds.

Major, B., Barr, L., Zubek, J., & Babey, S.H. (1999). Gender and self-esteem: a meta-analysis. In Bos, A.E.R., Muris, P., Mulkens, S., & Schaalma, H.P. (2006). Changing self-esteem in children and adolescents: a roadmap for future interventions. *Netherlands Journal of Psychology*, 62, 26-33.

McCubbin MA, & McCubbin III. Families coping with illness: the resiliency model of family stress, adjustment and adaptation. In Board, R., & Ryan-Wenger, N. (2000). State of the science on parental stress and family functioning in pediatric intensive care units. *American Journal of Critical Care*, 9 (2), 106-124.

McCubbin III, Thompson A.II, & McCubbin, M.A. *Family assessment: resiliency, coping and adaptation*. Madison, Wis: University of Wisconsin System Publishers; 1996.

Moons, P. (2004). *Quality of life in adults with congenital heart disease: Beyond the quantity of life*. Doctoral dissertation, Katholieke Universiteit Leuven, Belgium.

Moore, P., Moore, M., Blakeney, P., Meyer, W., Murphy, L., & Herndon, D. (1996). Competence and physical impairment of pediatric survivors of burns of more than 80% total body surface area. *The Journal of Burn Care and Rehabilitation*, 17, 547-51.

Naess, A., Halstensen, A., Nyland, H., Pedersen, S.H., Moller, P., Borgmann, R., et al. (1994). Sequelae one year after meningococcal disease. *Acta Neurologica Scandinavica*, 89(2), 139-142.

Netherlands Central Bureau of Statistics. (2001). *Standaard Beroepenclassificatie 1992: Editie 2001*. Voorburg/Heerlen: Netherlands Central Bureau of Statistics.

Netherlands Central Bureau of Statistics (2007). *Jaarboek onderwijs in cijfers 2007*. Voorburg/Heerlen: Netherlands Central Bureau of Statistics.

Pathan, N., Faust, S.N., & Levin, M. (2003). Pathophysiology of meningococcal meningitis and septicaemia. *Archives of Disease in Childhood*, 88, 601-607.

Perl, T.M., Dvorak, L., Hwang, T., & Wenzel, R.P. (1995). Long-term survival and function after suspected gram-negative sepsis. *JAMA*, 271(4), 338-45.

Pollack, M.M., Ruttimann, U.E., & Getson, P.R. (1988). Paediatric risk of mortality (PRISM) score. *Critical Care Medicine*, 16(11), 1110-1116.

Pope, S.J., Solomons, W.R., Done, D.J., Cohn, N., & Possamai, A.M. (2007). Body image, mood and quality of life in young burn survivors. *Burns*, 33, 747-755

Reijneveld, S.A. & Schene, A.H. (2001). Higher prevalence of mental disorders in Socioeconomically deprived urban areas in The Netherlands: community or personal disadvantage? *Journal of Epidemiology and Community Health, 55*(11), 847

Rey, A. (1964). *L'examen clinique en psychologie*. Paris: Presses Universitaires de France.

Rees, G., Gledhill, J., Garralda, M.E., & Nadel, S. (2004). Psychiatric outcome following paediatric intensive care unit (PICU) admission: a cohort study. *Journal of Intensive Care Medicine, 30*, 1607- 1614.

Rennick, J.E., Johnston, C.C., Dougherty, G., Platt, R., & Ritchie, J.A., (2002). Children's psychological responses after critical illness and exposure to invasive technology. *Developmental and Behavioural Pediatrics*, 23(3), 133-144.

Robert, R., Meyer, W., Bishop, S., Rosenberg, L., Murphy, L., & Blakeney, P. (1999). Disfiguring burn scars and adolescent self-esteem. *Burns*, 25, 581-585.

Robins, R.W., Trzesniewski, K.H., Tracy, J.L., Gosling, S.D., & Potter, J. (2002). Global self-esteem across the life-span. Psychology and Aging, 17, 423-434. In Bos, A.E.R., Muris, P., Mulkens, S., & Schaalma,

H.P. (2006). Changing self-esteem in children and adolescents: a roadmap for future interventions. *Netherlands Journal of Psychology*, 62, 26-33.

Saan, R.J., & Deelman, B.G. (1986). *The 15-Words Tests A and B (a preliminary manual)*. Groningen: University of Groningen, Department of Neuropsychology.

Sameroff, A.J. & Rosenblum, K.L. (2006). Psychosocial constraints on the development of resilience. *Annals New York Academy of Sciences,* 1094, 116-124.

Sharshar, T., Carlier, R., Bernard, F., Guidoux, C., Brouland, J.P., & Nardi, O. (2007). Brain lesions in septic shock: a magnetic resonance imaging study. *Intensice Care Medicine*, 33(5), 798-806.

Sharshar, T., Annane, D., Grandmaison de, G.L., Brouland, J.P., Hopkonson, N.S., & Gray, F. (2004). The neuropathology of septic shock. *Brain Pathology*, 14, 21-33.

Shears, D., Nadel, S., Gledhill, J., & Garralda, M.E. (2005). Short-term psychiatric adjustment of children and their parents following meningococcal disease. *Pediatric Critical Care Medicine*, 6(1): 39-43.

Shears, D., Nadel, S., Gledhill, J., Gordon, F., & Garralda, M.E. (2007). Psychiatric adjustment in the year after meningococcal disease in childhood. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46 (1), 76-82.

Shudy, M., Almeida de, L.M., Ly, S., Landon, C., Groft, S., Jenkins, T.L., et al. (2006). Impact of pediatric critical illness and injury on families: a systematic lliterature review. *Pediatrics*, 118(3), S203-S218.

Stochetti, N. (2005). Brain and sepsis: functional impairment, structural damage and markers. *Anesthesia and analgesia*, 101(5), 1463-4.

Stuart, J.M., Middleton, H., & Gunnell, D.J. (2002). Socioeconomic inequality and meningococcal disease. *Communicable Disease and Public Health*, 5(4), 327-328.

Stuber, M.L., & Shemesh, E. (2006). Post-traumatic stress response to life-threatening illnesses in children and their parents. *Child and Adolescent Psychiatric Clinics of North America*, 15, 597-609.

Sukankarat, K., Greer, S., Brett, S., & Williamson, R. (2007). Physical and psychological sequelae of critical illness. *British Journal of Health Psychol*, 12, 65-74.

Sundin, E.C., & Horowitz, M.J. (2003). Horowitz's Impact of Event Scale evaluation of 20 years of use. *Psychosomatic Medicine*, 65, 870-876.

Taylor, H.G., Mills, E.L., Ciampi, A., Berger du, R., Watters, GV., Gold, R., et al., (1990). The sequelae of Haemophilus Influenzae meningitis in school-age children. *The New England Journal of Medicine*, 323, 1657-1663.

Taylor, H.G., & Schatschneider, C. (1992). Academic achievement following childhood brain disease: implications for the concept of learning disabilities. *Journal of Learning Disabilities*, 25 (10), 630-8.

Taylor, H.G., & Alden, J. (1997). Age-related differences in outcomes following childhood brain insults: an introduction and overview. *Journal of the International Neuropsychological Society* , 3, 555-567.

Taylor, H.G., Schatschneider, C., Watters, G.V., Mills, E.L., Gold, R., MacDonald, N., et al. (1998). Acute-phase neurologic complications of Haemophilus influenzae type b meningitis: association with developmental problems at school age. *Journal of Child Neurology*, 13(3), 113-119.

Taylor, H.G., Schatschneider, C., & Minich, N.M. (2000). Longitudinal outcomes of Haemophilus influenzae meningitis in school-age children. *Neuropsychology*, 14(4), 509-518.

Taylor Jr., F.B., Toh, C.H., Hoots, W.K., Wada, H., & Levi, M. (2001). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thrombosis Haemostasis* , 86, 1327-1330.

Tick, N.T., Van der Ende, J., & Verhulst, F.C. (2008). Twenty-year trends in emotional and behavioural problems of Dutch children in a changing society. *Acta Psychiatrica Scandinavica*, 116 (6), 473-82.

Tick, N.T., Van der Ende, J., & Verhulst, F.C. (in press). *Ten-year increase in service use in the Dutch population.* Submitted for publication. *Social Psychiatry and Psychiatric Epidemiology* (2008).

Tomlinson, P.S., Harbaugh, B.L., Kotchevar, J., & Swanson, L. (1995). Caregiver mental health and family health outcomes following critical hospitalization of a child. *Issues in Mental Health Nursing*, 16, 533-545.

Törnqvist, J., Van Broeck, N., Finkenauer, C., Rosati, R., Schwering, K.L., Hayez, J.Y., et al. (1999). Long-term psychosocial adjustment following pediatric liver transplantation. *Pediatric Transplantation*, 3, 115-125.

Treffers, D.A., Goedhart, A.W., Veerman, J.W., Van den Bergh, B.R.H., Ackaert, L., & De Rycke, L. (2002). *Handleiding competentiebelevingsschaal voor adolescenten*. Lisse, The Netherlands: Swets & Zeitlinger.

Van Empelen, R., Jennekens-Schinkel, A., Rijen van, P.C., Helders, P.J., & Nieuwenhuizen van, O. (2005). Health-related quality of life and self-perceived competence of children assessed before and up to two years after epilepsy surgery. *Epilepsia*, 46, 258-271.

Vanheusden, K., Van der Ende, J., Mulder, C.L., Van Lenthe, F.J., Verhulst, F.C., & Mackenbach, J.P. (in press). The use of mental health services among young adults with emotional and behavioural problems: equal use for equal needs? *Social Psychiatry and Psychiatric Epidemiology (*2008).

Vanheusden, K., Mulder, C.L., Van der Ende, J., Van Lenthe, F.J., Mackenbach, J.P., & Verhulst, F.C. *Young adults face major barriers to seeking help from mental health services*. Submitted for publication.

Veerman, J.W., Straathof, M.A.E., Treffers, D.A., Van den Bergh, B.R.H., Ten Brink, L.T. (1997). Handleiding competentiebelevingsschaal voor kinderen. Lisse, The Netherlands: Swets & Zeitlinger.

Verhulst, F.C., Van der Ende, J., & Koot, H.M. (1996). *Handleiding voor de CBCL/4-18.* Rotterdam: Department of Child and Adolescent Psychiatry, Sophia Children's Hospital, Erasmus University Rotterdam.

Verhulst, F.C., Van der Ende, J. & Koot, H.M. (1997a). *Handleiding voor de Teacher's Report Form (TRF).* Rotterdam: Department of Child and Adolescent Psychiatry, Sophia Children's Hospital, Erasmus University Rotterdam.

Verhulst, F.C., Van der Ende, J., & Koot, H.M. (1997b). *Handleiding voor de Youth Self-Report (YSR).* Rotterdam: Department of Child and Adolescent Psychiatry, Sophia Children's Hospital, Erasmus University Rotterdam.

Vermunt, L.C.A.C., Buysse, C.M.P., Joosten, K.F.M., Oranje, A.P., Hazelzet, J.A., Verhulst, F.C., & Utens, E.M.W.J. (2008). Self-esteem in children and adolescents after septic shock caused by Neisseria meningitidis: scars do matter. *Journal of Adolescent Health*, 42 (4), 386-93.

Vermunt, L.C.A.C., Buysse, C.M.P., Joosten, K.F.M., Hazelzet, J.A., Verhulst, F.C., Utens, E.M.W.J. (2008). Behavioural, emotional and post-traumatic stress problems in children and adolescents long-term after septic shock caused by Neisseria meningitidis. *British Journal of Clinical Psychology, 47,251-263*.

Wallace, M., Harcourt, D., & Rumsey, N. (2007). Adjustment to appearance changes resulting from meningococcal septicaemia during adolescence: a quantitative study. *Developmental Rehabilitation*, 10(2), 125-132.

Wechsler D. (1991). *Manual for the Wechsler Intelligence Scale for Children- Third Edition.* San Antonio, TX: The Psychological Corporation.

Wernovsky, G., Wypij, D., Jonas, R.A., Mayer Jr., J.E., Hanley, F.L., Hickey, P.R. et al. (1995).Postoperative course and hemodyamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation*, 92, 2226-2235.

Wheeler, J.S., Anderson, B.J., & De Chalain, T.M. (2003). Surgical interventions in children with meningococcal purpura fulminans—a review of 117 procedures in 21 children. *Journal of Pediatric Surgery* , 38, 597-603.

Williams, R. (2007). The psychosocial consequences for children of mass violence, terrorism and disasters. *International Review of Psychiatry, 19* (3), 263-277.

Wray, J., & Sensky, T. (1998). How does the intervention of cardiac surgery affect the self-perception of children with congenital heart disease? *Child: Care and Health Development*, 24, 57-72.

Wyman, P.A., Cowen, E.L., Work, W.C., & Parker, G.R. (1991). Developmental and family milieu correlates of resilience in urban children who have experienced major life stress. *American Journal of Community Psychology, 19*, 405-426.

Youngblut, J.M., & Schiao, S-Y.P. (1993). Child and family reactions during and after pediatric ICU hospitalization: a pilot study. *Heart & Lung*, 22, 46-54.

Summary

Summary

The objective of the study described in this thesis was to investigate a range of long-term psychosocial outcomes of children, adolescents and young adults who survived septic shock, caused by *Neisseria meningitidis*, in childhood. In addition, psychological functioning of their parents was assessed.

In **chapter 1**, the background and the aims of this study were presented. This study was started to get insight into the long-term outcomes -both from a medical and a psychosocial point of view-, of having survived septic shock, caused by *Neisseria meningitidis*, in childhood. Septic shock, caused by *Neisseria meningitidis* with petechiae and/or purpura, also called Meningococcal Septic Shock (MSS), is the most serious form of meningcococcal infection in early childhood. MSS is often confused with MD, patients with septic shock show the clinical features of meningitis but in addition the cardiovascular collapse of a septic shock causes a more fulminant illness with a higher mortality rate. MSS is a life-threatening illness in mostly previously healthy children, with an unexpected and sudden onset, requiring immediate admission to a Paediatric Intensive Care Unit (PICU). Children with MSS are one of the most severely ill and unstable groups of children admitted to a PICU. A previously healthy child may die within 24 hours. The study described in this thesis focuses on the psychosocial outcomes.

In the present study, various indicators of psychosocial functioning of children, adolescents and young adults who survived MSS, and their parents, were measured. A follow-up examination was performed (from 2005-2006) among 136 consecutive surviving patients, who were admitted to the PICU of ErasmusMC-Sophia Children's Hospital between 1988 and 2001 (4-16 years ago). The present patient sample consisted of 136 patients, aged 6-31 years, and parents of 88 patients, aged 6-17 years. The main aims of the study were:

1. To compare the present psychosocial functioning, encompassing intellectual and neuropsychological functioning, behavioural and emotional problems, including posttraumatic stress problems, and self-esteem, of children and adolescents, and psychosocial functioning of young adults, who survived MSS, with that of normative samples.
2. To compare the present psychosocial functioning of both mothers and fathers of the patient sample with those of normative samples.
3. To determine the role of age at time of follow-up and gender on psychosocial functioning.
4. To examine the predictive value of age at time of illness, severity of illness and other medical variables on psychosocial functioning of the patient sample.

In **chapter 2** long-term cognitive functioning and its predictors were examined in children and adolescents who survived MSS. The Wechsler Intelligence Scale for Children-Third Edition (WISC-III) was used to measure intellectual functioning and neuropsychological tests were used to measure attention, verbal memory, visual-motor integration and executive skills.

Overall, results of the total MSS sample (N=77) as to neuropsychological functioning were similar to those of normative reference groups. On social and practical understanding and visual-motor integration, however, MSS children obtained poorer outcomes compared to normative data. Two children had mental retardation (estimated IQ <70) due to the MSS. The percentage of children with mental retardation or borderline intellectual functioning (15%) was similar to that in the general population (16%). Eighteen children (23%) had a Z-score<-2, indicating unusual poor functioning, on one or more domains of neuropsychological functioning (selective attention, sustained attention and executive functioning). Compared to normative data, significantly more children had received special education services in the past. Older age at time of follow-up was the most important significant predictor of poorer long-term cognitive functioning.

In conclusion, overall, long-term outcomes as to cognitive functioning of the total MSS sample were similar to those of normative reference groups, but MSS children showed long-term impairments on social and practical understanding, visual-motor integration, attention and executive functioning.

In **chapter 3** the occurrence of a wide range of behavioural and emotional problems, including post-traumatic stress problems, was assessed in children and adolescents long-term after MSS. Parents of 89 MSS children, aged 6-17 years, completed the Child Behavior Checklist (CBCL), teachers of 65 children same-aged MSS children completed the Teacher's Report Form (TRF) and 45 11-17-year-old MSS children completed the Youth Self Report (YSR). These data were compared with those from normative reference groups.

Overall, the proportions of MSS children scoring in the deviant range for problem behaviour were comparable to the proportions in the reference groups, according to parents', teachers' and self-reports. As to the level of emotional and behaviour problems, mothers of MSS children reported more somatic complaints regarding their children in comparison with the reference groups. Severity of illness was not a significant predictor of behavioural, emotional and post-traumatic stress problems. Age at time of illness was a significant predictor of behavioural, emotional and post-traumatic stress problems in MSS children, indicating that the younger the child at time of illness, the more problems were reported by parents at follow-up.

Overall, it was concluded that long-term behavioural, emotional and post-traumatic stress outcomes of MSS children, were comparable to those in the general population.

In **chapter 4** long-term self-esteem, and its relation with scars, amputations and orthopedic sequelae was investigated in 65 children and adolescents who survived MSS. The Dutch versions of the Self-Perception Profile for Children (SPP-C; 8-11 years) and the Self-Perception Profile for Adolescents (SPP-A; 12-17 years) were used to assess self-esteem. The Patient and Scar Assessment Scale (PSAS) was used to evaluate scar severity. MSS boys aged 8-11 years obtained higher, more favourable scores on self-esteem while same-aged MSS girls reported comparable levels of self-esteem compared to respectively same-aged reference boys and girls. MSS boys and girls aged 12-17 years obtained unfavourable scores on self-esteem compared to respectively same-aged reference boys and girls. Overall, gender did not have an effect on self-esteem. Severity of illness, age at time of illness and age at time of follow-up were not significant predictors of self- esteem. MSS adolescents with scars reported lower global self-worth than MSS adolescents without scars. The worse MSS children evaluated their scars, the worse their outcomes on social acceptance. The worse MSS adolescents evaluated their scars, the worse their outcomes on close friendship, but the better their outcomes on social acceptance and behavioural conduct.

In conclusion, for MSS children favourable outcomes on self-esteem were found, whereas MSS adolescents reported lower self-esteem compared to reference adolescents. Adolescents with scars reported lower global self-worth than MSS adolescents without scars.

In **chapter 5** long-term psychosocial outcomes of adults who survived MSS during childhood were investigated. These outcomes encompassed: biographical characteristics, illness-related physical or social consequences, intellectual functioning and behavioural and emotional problems. In total 58 MSS patients, aged 16-31 years, participated in this study. A semi-structured interview was used to assess biographical characteristics and illness-related physical or social consequences. A standardized intelligence test, the Groninger Intelligence Test 2 (GIT2) was used to assess intellectual functioning. The Adult Self-Report (ASR) was used to assess behavioural and emotional problems. Overall, MSS patients did not differ from reference groups as to biographical characteristics. The majority of MSS patients did not report illness-related physical or social consequences. Overall, intellectual functioning and levels of behavioural and emotional problems of MSS patients were comparable to those of the reference group.

It was concluded that long-term outcomes of adults as to biographical characteristics, illness-related physical or social consequences, behavioural and emotional problems and intellectual functioning were favourable.

In **chapter 6** long-term mental health and disease-related psychosocial limitations were investigated in parents of 88 children and adolescents who survived MSS. The General Health Questionnaire (GHQ-28) was used to assess mental health and a semi-structured interview to explore long-term disease-specific limitations for parents. Parents reported less psychiatric symptoms compared to reference groups. Severity of illness and age at time of illness were no significant predictors of parental mental health. The vast majority of parents reported no current psychosocial limitations due to the MSS. Seven percent of the parents decided not to have more children because of the MSS. One tenth of the parents reported that the current emotional burden because of the MSS is large.

In conclusion, favourable long-term outcomes on mental health were found in parents of children who survived MSS. Nevertheless a minority of parents still experiences current emotional burden and disease-related limitations.

In **chapter 7** the main findings and conclusions of this thesis were discussed. Overall, for MSS children, adolescents and young adults, favourable long-term outcomes on cognitive functioning, behavioural and emotional problems, including post-traumatic stress problems, and self-esteem were found. Unfavourable psychosocial outcomes were found on several neuropsychological domains and on self-esteem. MSS children and adolescents showed impairments on social and practical reasoning, visual-motor integration, attention and executive functioning. MSS adolescents, especially those with skin scarring, reported a lower self-esteem than reference adolescents. MSS parents showed favourable, even better than 'normal' outcomes as to mental health. Nevertheless a minority of parents experienced disease-related psychosocial limitations.

Our results indicated that male gender was a risk factor for behavioural and emotional problems and lower self-esteem in the MSS child-, adolescent and adult sample. Severity of illness, measured by the PRISM score, was not related to psychosocial functioning in MSS children, adolescents and adults, neither to mental health in their parents. Age at time of illness was not related to cognitive functioning and self-esteem in MSS children, adolescents and adults, neither to mental health in their parents. Within the MSS sample, younger age at time of illness was associated with more behavioural and emotional problems. As to age at time of follow-up it was concluded that, overall, MSS adolescents are more at risk for cognitive-, behavioural and emotional problems and a lower self-esteem than MSS children.

Based on results of this study and those of previous short-term studies described in literature it can be concluded that a short-term screening, for example at 3 months after MSS, with a special focus on PTSD symptoms in parents and behavioural and emotional problems in children, is to be recommended for clinical practice. In addition we recommend providing structured information about long-term outcomes, especially as to impairments on neuropsychological functioning and self-esteem to parents and teachers, to make them alert for recognizing these deficits.

Samenvatting

Samenvatting

De hoofddoelstelling van het in dit proefschrift beschreven onderzoek was het bestuderen van een reeks psychosociale uitkomsten op de lange termijn bij kinderen, adolescenten en jongvolwassenen die een septische shock, veroorzaakt door *Neisseria meningitidis*, op de kinderleeftijd overleefd hebben. Tevens werd het psychosociaal functioneren van hun ouders onderzocht.

In **hoofdstuk 1** werden de achtergrond en de doelen van het huidige onderzoek gepresenteerd. Dit onderzoek werd opgezet om inzicht te krijgen in de uitkomsten op de lange termijn, zowel vanuit een medisch als vanuit een psychosociaal perspectief, van het overleefd hebben van een septische shock, veroorzaakt door *Neisseria meningitidis*, op de kinderleeftijd. Septische shock, veroorzaakt door *Neisseria meningitidis*, met petechiën en purpura, ook wel Meningokokken Septische Shock (MSS) genoemd, is de ergste vorm van meningokokkeninfectie op de kinderleeftijd. MSS wordt vaak verward met meningitis (hersenvliesontsteking). Patiënten met septische shock hebben vaak de klinische kenmerken van meningitis, maar de cardiovasculaire collaps bij septische shock zorgt daarnaast voor een zeer heftige ziekte met een hogere morbiditeit en mortaliteit. MSS is een levensbedreigende aandoening die zich in voorheen meestal gezonde kinderen voordoet, met een onverwachts en plots begin, en onmiddellijke opname op een pediatrische intensive care afdeling (*Paediatric Intensive Care Unit*, PICU) is noodzakelijk. Kinderen met MSS vormen één van de meest zieke en onstabiele groepen kinderen die op de PICU opgenomen worden. Een voorheen gezond kind kan binnen 24 uur doodgaan. Het onderzoek dat in dit proefschrift staat beschreven, heeft zich op de psychosociale uitkomsten gericht.

In het huidige onderzoek werden verschillende indicatoren van psychosociaal functioneren gemeten bij kinderen, adolescenten en jongvolwassenen die een septische shock overleefd hebben en bij hun ouders. Een follow-up-onderzoek werd uitgevoerd (van 2005 tot 2006) bij consecutieve overlevende patiënten die tussen 1988 en 2001 opgenomen waren op de afdeling Intensive Care Pediatrie van het Erasmus MC-Sophia Kinderziekenhuis (4-16 jaar geleden). De huidige onderzoeksgroep bestond uit 136 patiënten tussen de 6 en 31 jaar, en ouders van 88 patiënten die tussen de 6 en 17 jaar oud waren.

De doelstellingen van dit onderzoek waren:

1. Het vergelijken van het huidige psychosociaal functioneren, wat betreft intellectueel en neuropsychologisch functioneren, gedrags- en emotionele problemen, inclusief posttraumatische stressproblemen, en zelfwaardering van kinderen en adolescenten, en het psychosociaal functioneren van jongvolwassenen, die MSS overleefd hebben met dat van normgroepen.
2. Het vergelijken van het huidige psychosociaal functioneren van zowel moeders als vaders van kinderen en adolescenten van de huidige onderzoeksgroep met dat van normgroepen.

3. Het bepalen van de rol van leeftijd ten tijde van follow-up en geslacht ten aanzien van het psychosociaal functioneren van kinderen, adolescenten en jongvolwassenen die MSS overleefd hebben en dat van hun ouders.
4. Het bepalen van de voorspellende waarde van leeftijd ten tijde van ziekte, ernst van ziekte en een reeks medische variabelen voor het psychosociaal functioneren op lange termijn bij kinderen, adolescenten en jongvolwassenen in de huidige onderzoeksgroep en hun ouders.

In **hoofdstuk 2** werden het cognitief langetermijnfunctioneren en de voorspellende waarde van een aantal medische variabelen onderzocht bij kinderen en adolescenten (6-17 jaar) die MSS hebben overleefd. De Wechsler intelligentietest voor kinderen (*Wechsler Intelligence Scale for Children,* WISC-III) werd gebruikt om intellectueel functioneren te meten en verschillende neuropsychologische tests werden gebruikt om aandacht, verbaal geheugen, visuomotorische integratie en executieve vaardigheden te meten. Over het geheel genomen waren de resultaten van de totale patiëntengroep (n = 77) op de intelligentietest en op de neuropsychologische tests vergelijkbaar met die van de normgroepen. Op sociaal en praktisch begrip en visuomotorische integratie echter behaalden de MSS-kinderen en -adolescenten lagere scores in vergelijking met normdata. Twee kinderen hadden een verstandelijke beperking (een geschat IQ < 70) ten gevolge van de MSS. Het percentage kinderen met een verstandelijke beperking (IQ < 70) of een benedengemiddelde intelligentie (IQ tussen 70 en 85) (15%) was vergelijkbaar met dat in de algemene populatie (16%). Achttien kinderen (23%) behaalden een Z-score < -2, wat een uitzonderlijk laag functioneren inhoudt, op één of meer domeinen van neuropsychologisch functioneren (selectieve aandacht, volgehouden aandacht en executieve functies). In vergelijking met normdata hadden relatief meer MSS-patiënten in het verleden speciaal onderwijs gevolgd. Een oudere leeftijd ten tijde van follow-up was de belangrijkste voorspeller van slechter cognitief functioneren op lange termijn.

Over het geheel genomen waren de langetermijnuitkomsten ten aanzien van cognitief functioneren van de totale MSS-patiëntengroep vergelijkbaar met die van de algemene bevolking. MSS-kinderen en -adolescenten lieten echter beperkingen zien op het gebied van sociaal en praktisch begrip, visuomotorische integratie, aandacht en executieve functies.

In **hoofdstuk 3** werd het vóórkomen van een groot aantal gedrags- en emotionele langetermijnproblemen, inclusief posttraumatische stressproblemen, bepaald bij kinderen en adolescenten die MSS hadden overleefd. Ouders van 89 kinderen, in de leeftijd van 6 tot 17 jaar, vulden de *Child Behavior Checklist* (CBCL) in over hun kinderen, leerkrachten van 65 kinderen van dezelfde leeftijd vulden de *Teacher's Report Form* (TRF) in en 45 11-17-jarige kinderen vulden de *Youth Self Report* (YSR) in. Deze gegevens werden vergeleken met die van referentiegroepen.

Over het geheel genomen waren de proporties van MSS kinderen met scores in het deviante gebied voor probleemgedrag vergelijkbaar met die van referentiegroepen, zowel wanneer de ouders, de leerkrachten als kinderen en adolescenten zelf de informanten waren.

Wat betreft het niveau van gedrags- en emotionele problemen: moeders van MSS-kinderen rapporteerden meer somatische klachten van hun kinderen dan moeders uit de normgroep. Ernst van ziekte was geen significante voorspeller van gedrags-, emotionele of posttraumatische stressproblemen. Leeftijd ten tijde van ziekte was een significante voorspeller van deze problemen bij MSS-kinderen. Dit betekent dat op lange termijn meer problemen werden gerapporteerd door ouders naarmate hun kind jonger was ten tijde van ziekte.

Geconcludeerd werd dat over het algemeen langetermijnuitkomsten wat betreft gedrags- en emotionele problemen, inclusief posttraumatische stressproblemen, voor MSS-kinderen vergelijkbaar waren met die van de algemene bevolking.

In **hoofdstuk 4** werd zelfwaardering, en de relatie tussen littekens, amputaties en orthopedische gevolgen enerzijds en zelfwaardering anderzijds, onderzocht bij 65 MSS-kinderen en -adolescenten. De Nederlandse versies van de *Self-Perception Profile for Children* (SPP-C:8-11 jaar) en de *Self-Perception Profile for Adolescents* (SPP-A:12-17 jaar), de *Competentie Belevingsschaal voor Kinderen* (CBSK, 8-11 jaar) en de *Competentie Belevingsschaal voor Adolescenten* (CBSA, 12-17 jaar), werden gebruikt om zelfwaardering te meten. De *Patient and Scar Assessment Scale* (PSAS) werd gebruikt om de ernst van littekens te evalueren. MSS-jongens van 8 tot en met 11 jaar oud rapporteerden een hogere zelfwaardering dan jongens van dezelfde leeftijd uit de normpopulatie, terwijl MSS-meisjes een zelfwaardering lieten zien die vergelijkbaar was met die van meisjes van dezelfde leeftijd uit de normpopulatie. MSS-jongens en -meisjes van 12 tot en met 17 jaar oud rapporteerden een lagere zelfwaardering dan hun seksegenoten van dezelfde leeftijd uit de normpopulatie. Over het geheel genomen werd er geen effect van geslacht op zelfwaardering gevonden. Ernst van ziekte, leeftijd ten tijde van ziekte en leeftijd ten tijde van follow-up bleken geen significante voorspellers van zelfwaardering. MSS-adolescenten met littekens rapporteerden een lager gevoel van eigenwaarde dan MSS-adolescenten zonder littekens. Hoe erger MSS-kinderen hun littekens beoordeelden, hoe lager hun zelfwaardering was wat betreft sociale acceptatie. Hoe erger MSS-adolescenten hun littekens beoordeelden, hoe lager hun zelfwaardering was op het domein van hechte vriendschap, maar hoe hoger het was ten aanzien van sociale acceptatie en gedrag.

Over het geheel genomen waren voor MSS-kinderen de uitkomsten ten aanzien van zelfwaardering gunstig, terwijl MSS-adolescenten een lagere zelfwaardering rapporteerden in vergelijking met leeftijdgenoten van de normpopulatie. MSS-adolescenten met littekens rapporteerden een lager gevoel van eigenwaarde dan MSS-adolescenten zonder littekens.

In **hoofdstuk 5** werden de psychosociale langetermijnuitkomsten onderzocht bij volwassenen die MSS in de kinderleeftijd overleefd hadden. Deze psychosociale uitkomsten omvatten biografische kenmerken, ziektegerelateerde fysieke of sociale gevolgen, intellectueel functioneren en gedrags- en emotionele problemen. In totaal deden 58 volwassenen tussen de 16 en 31 jaar mee. Een semigestructureerd interview werd gebruikt om biografische kenmerken en ziektegerelateerde fysieke of sociale gevolgen te meten. Een gestandaardiseerde intelligentietest, de *Groninger Intelligentie Test 2* (GIT2), werd gebruikt om intellectueel functioneren te meten en de *Adult Self Report* (ASR) werd gebruikt om gedrags- en emotionele problemen te meten. In het algemeen verschilden MSS-patiënten niet van normgroepen wat betreft biografische kenmerken. De meerderheid van de MSS-patiënten rapporteerde geen ziektegerelateerde fysieke of sociale gevolgen. In het algemeen beschouwd was het niveau van gedrags- en emotionele problemen en van intellectueel functioneren van MSS-patiënten vergelijkbaar met dat van de normpopulatie.

Geconcludeerd werd dat in het algemeen de langetermijnuitkomsten wat betreft biografische kenmerken, ziektegerelateerde fysieke of sociale gevolgen, intellectueel functioneren en gedrags- en emotionele problemen bij de MSS-volwassenen gunstig waren.

In **hoofdstuk 6** werden de geestelijke gezondheid en ziektegerelateerde psychosociale beperkingen onderzocht bij de ouders van 88 MSS-kinderen en -adolescenten. De *General Health Questionnaire* (GHQ) werd gebruikt om geestelijke gezondheid te meten en een semi-gestructureerd interview werd gebruikt om ziektespecifieke beperkingen voor ouders op de lange termijn in kaart te brengen. De ouders rapporteerden minder psychiatrische symptomen voor zichzelf dan bij referentiegroepen het geval was. Ernst van ziekte en leeftijd ten tijde van ziekte waren geen significante voorspellers van de geestelijke gezondheid van ouders. Door het overgrote merendeel van de ouders werden geen huidige psychosociale beperkingen ten gevolge van de MSS gemeld. Zeven procent van de ouders had besloten geen kinderen meer te krijgen vanwege de meegemaakte MSS, en 10% van de ouders rapporteerde dat de huidige emotionele last ten gevolge van de MSS nog steeds groot was.

Geconcludeerd werd dat in het algemeen de langetermijnuitkomsten gunstig waren voor de ouders van kinderen die MSS overleefd hadden. Daarentegen was er een kleine minderheid van de ouders die nog steeds emotionele last en ziektespecifieke beperkingen ten gevolge van de MSS ervoer.

In **hoofdstuk 7** werden de belangrijkste bevindingen en conclusies van dit proefschrift besproken. In het geheel beschouwd werden er voor kinderen, adolescenten en jongvolwassenen die MSS overleefd hadden gunstige langetermijnuitkomsten gevonden wat betreft cognitief functioneren, gedrags- en emotionele problemen, inclusief posttraumatische stressproblemen, en zelfwaardering. Ongunstige uitkomsten werden gevonden op verschillende neuropsychologische gebieden en ten aanzien van zelfwaardering. MSS-kinderen en -adolescenten lieten beperkingen zien op de gebieden sociaal en praktisch begrip, visuomotorische integratie, executieve functies en aandacht. MSS-adolescenten, vooral degenen met littekens, rapporteerden een lagere zelfwaardering dan adolescenten uit de normpopulatie. Ouders lieten gunstige, zelfs 'betere dan normale' psychosociale uitkomsten zien wat betreft hun geestelijke gezondheid. Daarentegen ervoer een minderheid van de ouders nog steeds ziektegerelateerde psychosociale beperkingen.

Uit onze resultaten bleek dat mannelijk geslacht een risicofactor was voor gedrags- en emotionele problemen en voor een lagere zelfwaardering bij de MSS-kinderen, -adolescenten en -jongvolwassenen. Ernst van ziekte en leeftijd ten tijde van ziekte waren niet gerelateerd aan het psychosociaal functioneren van MSS-kinderen, -adolescenten en -volwassenen, noch aan de geestelijke gezondheid van hun ouders. Binnen de MSS-patiëntengroep bleek: hoe jonger ten tijde van ziekte, hoe meer gedrags- en emotionele problemen op lange termijn. Wat betreft leeftijd ten tijde van follow-up kon geconcludeerd worden dat MSS-adolescenten meer risico lopen op cognitieve, gedrags- en emotionele problemen en op een lagere zelfwaardering dan MSS-kinderen.

Op basis van de resultaten van dit onderzoek en van eerder uitgevoerde kortetermijnstudies, beschreven in de literatuur, kan geconcludeerd worden dat een screening op korte termijn, bijvoorbeeld drie maanden na de MSS, gericht op symptomen van posttraumatische stressstoornis bij ouders en op gedrags- en emotionele problemen bij kinderen, aan te bevelen is voor de klinische praktijk. Tevens adviseren wij om gestructureerde informatie aan te bieden aan ouders en leerkrachten over de mogelijke psychosociale gevolgen van MSS op de lange termijn, vooral over de beperkingen in neuropsychologisch functioneren en op het gebied van zelfwaardering, zodat zij alert kunnen zijn om deze beperkingen tijdig te signaleren.

Dankwoord

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Lindy

Curriculum Vitae

Curriculum Vitae

Lindy Cornelia Anna Catharina Vermunt werd op 27 april 1982 geboren te Oud en Nieuw Gastel. In 2000 behaalde zij haar VWO-diploma aan het Markland College te Oudenbosch. In datzelfde jaar startte zij haar studie Psychologie aan de Universiteit van Tilburg, waar zij in november 2004 afstudeerde (major richting: Kind en Jeugd, minor richting: Leren en Cultuur). Van september 2003 tot juli 2004 liep zij stage op het Medisch Kleuter Dagverblijf te Gorinchem, waar zij klinische ervaring opdeed bij jonge kinderen met ontwikkelingsproblematiek. Haar afstudeeronderzoek richtte zich op kindertekeningen, met name de validering van twee scoringssystemen voor gedrags- en emotionele problematiek aan de hand van de menstekening.

Van september 2005 tot juli 2006 was zij part-time werkzaam bij een vrijgevestigde psychologen praktijk (genaamd Guelen) te Oudenbosch. Daar verrichte zij als psycholoog zowel psychodiagnostiek als behandeling bij kinderen en adolescenten tussen de 5 en 18 jaar met uiteenlopende problematiek.

In maart 2005 werd zij als junior psycholoog aangenomen op het Erasmus MC-Sophia Kinderziekenhuis voor het uitvoeren van de dataverzameling van een onderzoek naar het lange termijn psychosociaal functioneren van kinderen, adolescenten en jongvolwassenen die septische shock hadden overleefd. Dit onderzoek werd uitgevoerd in een samenwerkingsverband tussen de afdelingen Kinder- en Jeugdpsychiatrie en Intensive Care Pediatrie van het Erasmus MC-Sophia. Vanaf 2006 werd de dataverzameling van het onderzoek naar overlevenden van septische shock voortgezet in een promotietraject onder begeleiding van haar promotor prof. dr. Frank Verhulst en onder dagelijkse begeleiding van dr. Elisabeth Utens, haar copromotor. Bovendien werd dit een dubbel-promotie, intensivist Corinne Buysse verzamelde tegelijkertijd data over de medische uitkomsten bij deze kinderen en beschreef haar resultaten in haar proefschrift, onder begeleiding van haar promotor prof. dr. Dick Tibboel en onder dagelijkse begeleiding van dr. Koen Joosten, tevens copromotor van Lindy. De onderzoeksresultaten van de studie naar de psychosociale uitkomsten op lange termijn bij patiënten die op de kinderleeftijd een septische shock overleefd hebben staan beschreven in dit proefschrift.