Child and parental adaptation to pediatric oncology

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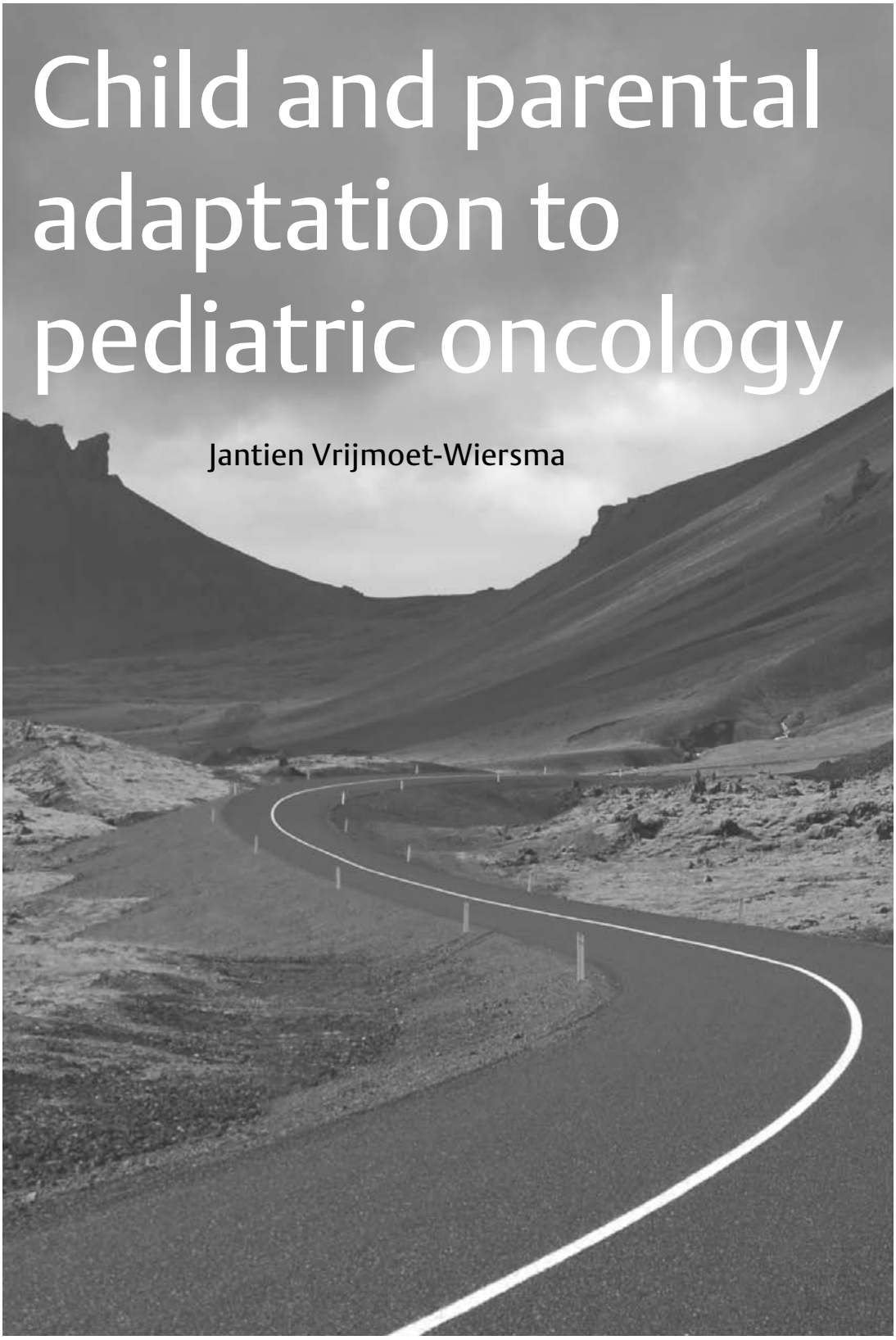

Child and parental adaptation to pediatric oncology

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1

Introduction

Introduction

Parental reactions to childhood cancer [32,33,87] and health-related quality of life of pediatric cancer patients [75] have been the focus of extensive research in the past two decades. In the Introduction of this thesis, first a general overview will be given of the incidence, survival and treatment of pediatric cancer, followed by a paragraph on stem cell transplantation (SCT), a specific treatment for a subgroup of patients. Late effects of cancer treatment and SCT are also presented. Next, the area of pediatric psychology and specific relevant themes will be presented, followed by a discussion of parental reactions to childhood cancer, as well as issues on health related quality of life (HRQoL) in children with cancer, children undergoing SCT and children suffering from a rare and complicated disease called Langerhans Cell Histiocytosis (LCH). Determinants, risk and protective factors of parental reactions to childhood cancer will be described and research areas that are understudied until now will be identified.

Medical aspects

Pediatric Oncology

In the Netherlands, approximately 500 children are diagnosed with cancer annually [21,85]. Most common childhood cancer diagnoses are leukemia (30%), followed by brain tumors (25%), lymphoma, solid tumors (e.g. renal cancers, osteosarcoma, Ewing sarcoma etc.). Treatment of childhood cancer takes place in one of the seven pediatric oncology centres in the Netherlands. Patients are treated according to (inter)national treatment protocols, which consist of regimens of chemotherapy and in some cases radiation therapy or surgery. Treatment duration can range from a few months (e.g. in the case of Non-Hodgkin Lymphoma) to two years (in the case of acute lymphatic leukaemia (ALL).

Cancer treatment has many side effects, such as hair loss, nausea, loss of appetite, diarrhea and oral mucositis (mouth sores), which is painful and can inhibit eating, drinking and taking oral medication. Due to low blood counts, children are very susceptible to infections and thus are forced to live with restrictions for a long period of time (i.e. not going to school or to crowded places like shops or public transportation). Part of the treatment of solid tumors in children consists of surgery, in some cases this involves amputation or rotation plasty, which causes lasting and visible limitations and the need to revalidate for a long period. Brain tumors require neurosurgery, which often results in neurological, endocrine and psychological side effects.

Treatment protocols have become more effective in the past decades and the duration of clinical treatment has shortened considerably in favour of treatment through outpatient clinics. Five-year survival rates have grown to 70-75%, whereas in the 1960s, only 30% of children with cancer had a 10 year event-free survival [21,76]. Children with ALL, Wilm's tumor and lymphoma generally have the best chances of survival (above 85%) [84], whereas children with Acute Myeloid Leukemia (AML) [31], bone tumor [52], brain tumor [49] or neuroblastoma [88] have a worse prognosis.

Stem cell transplantation

For children with high risk ALL or relapsed malignancies and inborn errors of metabolism, stem cell transplantation (SCT) is a treatment of last resort. In the Netherlands, approximately 60 children are transplanted per year, most of them in the Leiden University Medical Center (30-40), followed by the Wilhelmina Children's Hospital Utrecht (20-30). About ten pediatric transplantations take place in the University Medical Center Nijmegen. The treatment involves high doses of chemotherapy and/or total body irradiation before the stem cells of a donor are infused [55]. If possible, one of the siblings of the ill child will act as a matched donor; if not, an unrelated matched donor will be searched through an international donor base. Stem cell transplantations are usually performed with bone marrow from a donor (allogeneic) but in some instances take place with cells from the patient itself (autologous). In Europe, one in four allogeneic transplants is now performed with marrow from an unrelated donor [80]. If that possibility fails too, parents can act as a haploidentical donor for their child. In recent years and only in a limited number of countries, the possibility exists for parents to perform embryo selection in order to conceive another child with the right haploidentical match to act as a sibling donor for the patient. The debate is whether it is ethical to conceive a 'designer baby' to act as a donor for an ill sibling.

Stem cell transplantation is a hazardous treatment, associated with high morbidity and mortality [17], because children become extremely susceptible to infections, due to high doses of chemotherapy to eradicate any present malignant cells and to suppress the body's natural inclination to reject the donor cells. It involves a lengthy hospital admission in an isolated, germ-free environment during a period of 8-12 weeks. Complications can arise when children suffer from potentially fatal infectious diseases such as adenovirus infections, aspergillus or veno-occlusive disease (VOD): swelling of blood vessels in the liver which causes blocks in the blood flow.

In the first four to six months post-SCT, children are still prone to develop infections and are forced to live with restrictions. They cannot return to school yet and need to avoid crowded places and certain types of food. Re-admissions due to complications (e.g. graft-versus-host disease (GVHD), which is a common complication

of allogeneic SCT in which functional immune cells in the transplanted marrow recognize the recipient as "foreign" and mount an immunologic attack, infections or graft rejection), loss of appetite and chronic fatigue are seen in many children in the first months post-SCT, which places a burden on parents and families.

Langerhans Cell Hystiocytosis

Langerhans Cell Hystiocytosis (LCH) is a rare and serious non-malignant disease that can manifest itself in diverse ways. LCH is the result of an abnormal proliferation of pathologic Langerhans cells, accompanied by other inflammatory cells in various tissues. The lesions are destructive, and healing results in scarring and fibrosis [6,57]. Symptoms can range from a single bone lesion to a life threatening multi-system disorder. The peak onset of LCH is between 1 and 4 years, although it can occur at any age [18]. The incidence is low: 4.1 cases per million per year, which means 15-18 newly diagnosed pediatric cases in the Netherlands every year [73].

LCH-treatment depends on the extent of the disease. Localised disease might be treated with local therapy, including the application of corticosteroids or surgical curettage. In case of disseminated LCH, chemotherapy is often the backbone of treatment [2]. Leiden University Medical Center is one of the expert institutes in the Netherlands on LCH. Whether LCH should be considered a malignant disease is a matter of debate [78]

Late effects

As increasing numbers of children with cancer survive, more attention has been devoted to describing and monitoring the late effects of the disease and treatment [74]. Late effects or sequelae of cancer treatment have been described in terms of physical effects [62], cognitive effects [54], social – and emotional problems [44], effects on health-related quality of life (HRQoL) and the attainment of developmental milestones [74]. The World Health Organisation (WHO) defines HRQoL as 'the individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns'. Long-term survivors of pediatric cancer are more likely to have diminished health status and to die prematurely than are adults who never had childhood cancer [38]. The risk of chronic health conditions is high, particularly for second malignancies, cardiovascular disease, renal dysfunction, severe musculoskeletal problems and endocrinopathies [22,62]. Cranial radiation in pediatric patients with a brain tumor has been shown to have serious consequences for attention/concentration and working memory and, as a result, a decline in intelligence [13]. Whether treatment with chemotherapy alone, now the standard treatment for children with ALL, has a detrimental effect on cognitive functioning is still a matter of debate [30,53], but recent findings show evidence of subtle long-term neurocognitive

effects on attention and executive functioning, while global intellectual functioning is generally preserved [12].

Following SCT, parents and children are faced with the risk of recurrence, chances of chronic graft-versus-host disease (GVHD) and numerous possible late effects such as pulmonary complications, growth problems and infertility [16,42,43,51]. In a recent Dutch study, the cumulative incidence of late effects in SCT-survivors was 93% after a median follow-up time of 7 years [10]. Neurocognitive problems following SCT have not been found in a large recent study among SCT survivors with miscellaneous underlying diseases [66], but children with severe congenital immunodeficiencies do appear to have an increased risk of long-term cognitive difficulties [81]. Fatigue can be a long-lasting problem, but the most worrying sequel to SCT is the high risk of secondary malignancies [43].

Children who have been treated for a complicated non-malignant disease like Langerhans Cell Hystiocytosis (LHC) can suffer from sequelae like Diabetes Insipidus (with a cumulative risk of 26%, 14 years after diagnosis [24]), growth retardation, hearing loss, physical problems, neurological problems (such as ataxia, learning difficulties and intellectual impairment [24,57]).

Pediatric psychology

Pediatric psychology, a fairly new area of expertise, addresses the range of physical and psychological development, health and illness affecting children, adolescents and their families [69]. Pediatric psychologists strive for a combination of research and patient care: science has informed practice in the field and practice has led to important questions that subsequently were put to the test of scientific inquiry [1]. Screening and assessment are hot topics among pediatric psychologists, who are keen on finding the most appropriate assessment instrument to determine which parents and children are most at risk to develop severe stress symptoms. The problem is that many instruments focus on different psychological domains, which also have common characteristics. Reliability and validity of several instruments have not been studied well [50]. Furthermore, there appears to be a split between the measures used in research and those used in clinical practice [14]. There does seem to be consensus about the need to combine generic questionnaires (with the possibility to compare to healthy norm data) with disease-related and disease-specific questionnaires, but the choice for a particular measure is not easily made. The availability of disease-related or disease-specific assessment measures is low in non-English speaking countries and this implies that (back) translation and cross-cultural validation of questionnaires is necessary. The translation in another language

and culture is a lengthy and laborious process and is not always carried out adequately and/or documented properly in research articles [83].

Once the parents most in need have been identified, interventions are needed to reduce distress and to teach parents adaptive coping or problem-solving skills. Pediatric psychologists have proved their worth in designing and applying cognitive-behavioral techniques, problem-solving skills and relaxation skills to help parents cope with their child's illness and its treatment. However, the effects of psychological interventions have scarcely been studied; hence the number of evidence based treatment programs is low. There is a need to evaluate treatments, combinations of modalities, moderators that affect outcome and the processes responsible for change [89]. In the last years, a number of promising intervention programs have been piloted to support parents of children newly diagnosed with cancer [26,34,71,72]. However, results of these studies vary, due to many methodological challenges, such as a low participation rate and early drop out because of unforeseen illness complications.

Psychological aspects

Alongside with fast and promising medical developments in the past decades, more attention has been devoted to counseling patients and families in dealing with the stress of diagnosis, treatment and survival of serious childhood illness. An increased emphasis has been placed on the recognition of psychological and social factors in the individual's (and one's family's) experience of illness and the inclusion of these factors on the development of interventions that can alleviate illness-related symptoms and adverse health outcomes [11].

Parental reactions to pediatric cancer

When parents are confronted with a cancer diagnosis in their child, they often report to feel as if 'their world has fallen apart'. Parents will enter a process of coping, sometimes referred to as an 'unexpected career' [4], because parents are able to show tremendous commitment and competence in caring for their child [8]. Parental stress reactions, (most often operationalized as anxiety, depressive symptoms, uncertainty or posttraumatic stress symptoms, PTSS) is high in most of the parents around the time of diagnosis [7,34]. These emotional manifestations of strain decrease to near normal levels over time in the majority of the parents, but have been found to persist in a substantial proportion of the parents, even many years post-treatment [87].

The psychosocial consequences of the child's illness on parents are best understood in light of contributions of the nature and severity of the child's illness, other

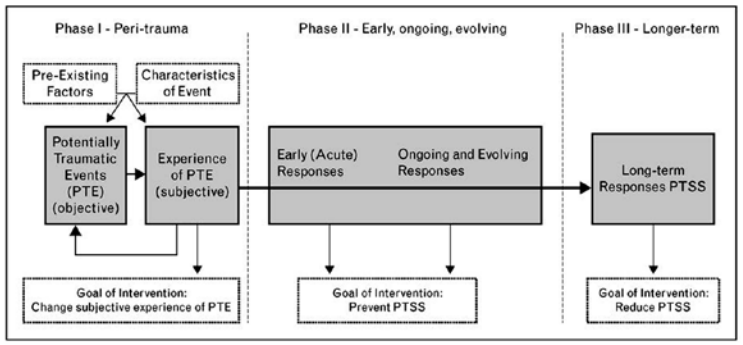
stressors in the family's life, characteristics of the family system, and the parent's coping strategies and capabilities [89]. Risk factors of poor adjustment are found in terms of illness complication factors [28] or demographic factors: parents of children with cancer who are less educated and parents with lower SES [29], single mothers and parents with a 'perceived unsatisfactory financial status' [45] report more depressive symptoms. However, psychological factors seem to have the greatest impact on parental adaptation to childhood cancer. Parents who display the most and highest levels of emotional manifestations of strain at diagnosis continue to experience the highest levels of symptoms, even after treatment ends [87]. Furthermore, pre-existing psychopathology [35,47] and trait anxiety have been identified as predictors of post-treatment PTSS for mothers [9] and fathers [27]. Child behavior problems [7] were found to be predictive of parental depressive symptoms. High levels of care giving demands, past traumatic life events, and less perceived social support [61] have also been identified as risk factors for the development and maintenance of emotional manifestations of parental strain.

One of the most frequently used models to understand the experience of families throughout the course of their child's illness, supported by a growing database of empirical research, is the Medical Traumatic Stress Model [35,36], see Figure 1 (published with permission of the original author, A.E. Kazak). The model contains three stages, i.e. peri-trauma (I), during treatment (II) and long-term sequelae (III). Medical events that may be traumatic (i.e. diagnosis itself, sudden admissions to the intensive care, medical complications) are referred to as Potentially Traumatic Events (PTEs). The term 'potentially traumatic' is used to underscore that events in itself are not necessarily traumatic, but the subjective interpretation of an event can make a particular event traumatic, or not. Phase I, the time around diagnosis, confronts parents with learning that their child has a serious and life-threatening illness. It involves treatment initiation, waiting for test results and taking practical decisions regarding the other children at home. Phase II is the period of time during treatment. It is variable in length and course and continues to expose patients and families to ongoing PTEs (e.g. side effects or complications of treatment, pain, death of other children on the ward, concerns about relapse or relapse itself). Phase III refers to the period after the cessation of treatment. It can involve long-term traumatic stress and sequelae and it includes both families of survivors and families of children who have died. Fear of a relapse, also termed as 'the Damocles syndrome' can linger for a long time in both parents and children [3,37].

Although cancer is an uncontrollable stressor, parents deal with the demands of the situation through actions, behaviors and thoughts, also referred to as coping [41]. Therefore, the experience of a trauma reaction due to childhood cancer is not always a pathological response. In fact, avoidance behavior seems to be functional in the early phase of childhood cancer when parents are overwhelmed with stressors and re-

experiencing is a natural way of processing and resolving difficult experiences. However, in face of active treatment and maintenance, avoidant parental behavior has been related to elevated levels of emotional manifestations of strain e.g., anxiety and depression [27,60]. Hence, only when the 'reexperiencing' or 'avoidance' reactions are extreme, distressing and persistent, they will fall into the area of pathology like Posttraumatic Stress Disorder (PTSD) or Acute Stress Disorder (ASD).

Figure 1. An integrative model of pediatric medical traumatic stress



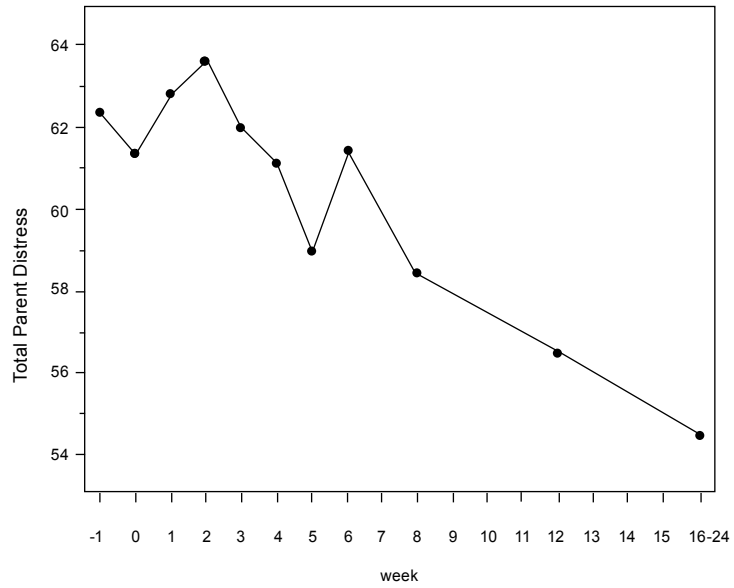
Source: Kazak AE, Kassam-Adams N, Schneider S, Zelikovsky N, Alderfer M, Rourke M. An integrative model of pediatric medical traumatic stress. J Pediatr Psychol 2006; 31: 343–355.

Parental reactions to SCT

Highest levels of parental stress are reported in the period preceding SCT and during the acute phase [86]. Sean Phipps and his study group have assessed parental stress in a longitudinal design from admission for SCT until 24 weeks post-SCT. They found that stress levels decrease steadily in the weeks and months after discharge in most parents [65], see Figure 2 (published with permission of the original author). However, in a subgroup of parents, stress levels still remain elevated for years post-SCT. Risk factors for long-term parental stress are socio-demographic and illness-related factors, such as being a mother [47], having lower socio-economic status (SES) [65] and the number of ICU transfers [48]. Furthermore, parental coping and adjustment at the time of SCT predict psychological functioning later on, e.g. a mother's appraisal of threat to her child's life [17,46] and maternal symptoms of anxiety and depression at admission and during hospitalization [46,47] are identified as predictors of stress post-SCT.

Only one study has been devoted to long-term parental stress reactions post-SCT [20] so far. Results of this qualitative, interview-based study showed that parents still worry about late effects of treatment, the risk of secondary malignancies, their child's

Figure 2. Parent SCT-related distress over time



infertility and their child's psychosocial well-being. Many parents report that their child's illness and treatment is still a source of anxiety, four to eight years post-SCT.

Perceived vulnerability

When parents are confronted with a life-threatening disease or a near-fatal accident of their child, they might react with a long lasting fear of losing their child, even if the immediate threat has disappeared or faded. Green and Solnit [23] introduced the term 'perceived vulnerability' to describe excessive parental anxiety and worrying about a child's health. They suggested that this anxiety often leads to a maladaptive pattern of parent-child interactions and child behavior problems, called the 'vulnerable child syndrome' [79]. Increased perceptions of child vulnerability are related to increased social anxiety and illness uncertainty in children with chronic illness [5,56]. Parents of children on treatment for cancer have shown elevated levels of perceived vulnerability and these perceptions are a significant predictor of child emotional adjustment [15]. In the context of SCT with a long period of uncertainty, perceptions of vulnerability may exist. This has not been studied yet.

Children's reactions to cancer

How children react to diagnosis and treatment for cancer is a widely researched area. The concept that has been studied most during the last years is health-related quality

of life (HRQoL). HRQoL includes different aspects of life, including physical functioning, psychological and social functioning. Children with cancer report a significantly lower HRQoL shortly after diagnosis, consisting of physical complaints, reduced basic motor functioning and autonomy and impaired global positive emotional functioning [39]. One year post diagnosis, most of the children (or their parents who act as proxy-reporters) show a significant improvement of HRQoL [19], but a proportion of the children still report lowered motor functioning and lowered positive emotional functioning [39].

Despite the obvious challenges and trauma cancer treatment can pose on children, the prevalence of psychopathology or social dysfunction is similar to that found in the general population or appropriate comparison groups, suggesting 'hardiness' in children and adolescents with cancer [59]. In numerous studies, children with cancer even report lower levels of affective distress than healthy children [67,68].

Children's reactions to SCT and LCH

Children undergoing SCT report low HRQoL scores during the acute phase, due to low levels of activity, mood disturbance and somatic distress consisting of nausea, mucositis and other physical complaints [64,70]. Within 4–6 weeks post-SCT, distress declines to levels lower than those seen at the time of admission, and a return to a presumed baseline level occurs within 4–6 months post-SCT [64]. As survivors reach 6 months to a year posttransplant and begin to reintegrate into their normal lifestyles, they show some mild disturbances in their self-concept and social functioning [63]. Long-term survivors of pediatric SCT report a 'good' or 'adequate' quality of life [25,58,82], when assessed after 3-5 years. Children report higher HRQoL scores than adult survivors of SCT, possibly due to the lower incidence of chronic graft-versus-host-disease in children [43]. However, a recent study among adult survivors of pediatric SCT showed that they were less satisfied with their physical health, general health, partner relations and sexual function [44].

HRQoL research in pediatric LCH patients is still scarce. In a recent study, more than 50% of the pediatric LCH patients reported a lowered HRQoL [57], especially in the domain 'emotional functioning'. Another study, performed with patients with bone lesions only found no differences in HRQoL with healthy peers [40].

Conclusion

The overview of the literature shows that considerable research has been conducted in the area of child and parental adaptation to cancer, SCT and LCH. However, less attention has been paid to some particular issues:

The availability of psychometrically sound disease-related assessment measures in the Dutch language is low. Most researchers in the Netherlands use non-illness specific questionnaires to assess levels of anxiety, depressive symptoms or PTSS in parents of children with a serious illness. The advantage of these measures is that results can be compared with other international studies more easily, but the disadvantages are that parents are considered to report symptoms of psychopathology. It would be better to consider parental adjustment to childhood illness as a normative process involving additional daily responsibilities, limitations in major life roles and increased strain in close relationships. Hence, there is a clear need of psychometrically sound disease-related and disease-specific measures in Dutch. The Pediatric Inventory for Parents (PIP) seems to be an adequate disease-related measure to use with parents of children with various illnesses. The psychometric qualities of this instrument have been studied by the original author [77], but a factor analysis has not been done yet.

The assessment of parental distress or parenting stress in relation to pediatric SCT is usually performed in itself, without the assessment of HRQoL in children. It would be interesting to find out if the concepts of HRQoL and parenting stress are related and if time since SCT is of influence on parenting stress. If so, this calls for a need of strategies for parents to reduce their own parenting stress and to deal with their child's well-being at the same time.

No quantitative data have been published to this date about long-term parental stress and adaptation post-SCT; all but one (qualitative) study in this area stopped assessing parents after 18 months post-SCT. This finding is surprising, considering the high incidence of late effects in this group. It is to be expected that parents will continue to worry about their child's health and future beyond the period of 18 months post-SCT. Until now, the concept of perceived vulnerability has not been assessed yet in parents of children undergoing SCT, which is unfortunate, because this concept could shed more light on the thoughts and perceptions of parents of long-term survivors and guide psychosocial and psychoeducational interventions.

To examine the psychological effects of a complex illness like LCH in pediatric patients, it is important to study not just HRQoL, but also behavioral aspects and cognitive functioning as well as the interactions between all three aspects. Until now, no study has combined all of these aspects.

Aims of the studies

The aim of the studies included in this thesis was to obtain better insight in psychological reactions of parents and children to the childhood cancer experience, SCT and LCH. We were interested in identifying outcomes and determinants of parental stress and adaptation processes. Specifically, the aims of the studies were:

- to gain more knowledge of the existing literature on parental reactions to childhood cancer and SCT and the way stress is operationalized and assessed.
- to assess disease-related stress in parents of children with cancer by using a newly translated disease-related measure of parental distress. We also aimed to evaluate the psychometric qualities of the instrument.
- to study the relationship between parenting stress and (child and) parent reported HRQoL before and after SCT.
- to assess long-term psychological consequences of pediatric SCT on parents and
- to assess a combination of emotional, behavioral and cognitive effects of the disease and its treatment in LCH survivors.

Outline of the thesis

In *Chapter 2*, results from a review study of 67 articles on stress and adaptation in parents of pediatric cancer patients are reported. *Chapter 3* describes the results of a multicenter study among parents of children on treatment for cancer. The aim of this study was to evaluate the psychometric qualities of the Dutch version of a disease-related instrument measuring parental stress, the Pediatric Inventory for Parents. *Chapter 4* is a review article on parental stress and adaptation among parents of children undergoing stem cell transplantation (SCT). *Chapter 5* contains the results of a longitudinal study on child- and parent reported health related quality of life and parenting stress in parents of children undergoing SCT, before admission and on average 10 months after discharge.

In *Chapter 6*, the results of a cross-sectional study on parental (disease-related and general) stress and perceptions of child vulnerability in parents of children who underwent SCT either 5 or 10 years ago are reported. In *Chapter 7*, cognitive problems, behavior problems and health related quality of life issues of children with Langerhans Cell Hystiocytosis (LCH) are described. *Chapter 8* is formed by the summary and general discussion and *Chapter 9* contains the Dutch summary of this thesis. In *Chapter 10*, the word of thanks, curriculum vitae and the list of abbreviations can be found.

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Assessment of Parental Psychological Stress in Pediatric Cancer: A Review

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Abstract

Goals of work. We present an overview of the literature between 1997 and 2007 on parental stress reactions following the diagnosis of childhood cancer and we evaluate methodological strengths and weaknesses of the studies. *Methods*. PubMed, PsychInfo and Cinahl databases were used. Sixty-seven were included in the review. *Results*. The conceptualization of parental stress and timing of assessment varies considerably between the studies, which makes comparison difficult. Most emotional stress reactions are seen around the time of diagnosis, with mothers reporting more symptoms than fathers. As a group, parents seem relatively resilient, although a subset of parents reports continuing stress even up to five years or more post diagnosis. *Conclusions*. The authors recommend clear definitions of parental stress, fixed points in time to assess parental stress and an approach that highlights both parental strengths and weaknesses. Improved assessment can contribute to tailoring psychological care to those parents most in need.

Introduction

The diagnosis of childhood cancer is one of the most intense, disruptive and enduring experiences that parents can have. The often unexpected and life-threatening diagnosis and the initiation of invasive medical treatment and its sequelae interfere with the entire family's normal activities and routines for a long period of time and impose stressors of varying duration, predictability and impact [25,42,58]. Since substantial progress has been made in cancer treatment and coordination of care, types of cancers that were once regarded as fatal are presently curable with treatment and have instead become chronic life-threatening diseases [17,78]. Nowadays, three out of four children diagnosed with a malignancy will survive their disease and treatment [24].

When parents are confronted with a diagnosis of cancer in their child a process starts, referred to as psychological stress [20,58,88]). In the literature, definitions of core elements of psychological stress vary considerably, often depending on the underlying theory [62].Much research has been focused on stress reactions observed in emotional manifestations of strain (anxiety, depressive symptoms) and more situation-specific emotional manifestations of strain (uncertainty, helplessness, loneliness and disease-related worry concerning future health and recurrence of the disease) [25,58,78]. Furthermore, a growing body of research has suggested that the impact of childhood cancer on the parents can well be conceptualized in terms of trauma-related symptoms or posttraumatic stress symptoms [33,82]. The outcome of the psychological stress process is generally referred to as adjustment [25,58]. The current review is based on the theory on stress and coping by [47]: when parents are confronted with a cancer diagnosis in their child (i.e. the stressor), a process starts, involving the appraisal of the stressor, followed by strain, (i.e. pressure or demand), and stress reactions, or the manifestations of strain, which become manifest as uncertainty, anxiety, depressive symptoms and posttraumatic stress symptoms.

The aims of the present review are, first, to evaluate the methodological strengths and weaknesses of studies on the emotional manifestations of strain in parents of children who have been diagnosed with cancer. Secondly, we will describe the prevalence and nature of parental strain according to disease phase (diagnosis, active treatment, maintenance and long-term survival), gender differences and risk and protective factors. Throughout the review article, we will group parental stress reactions into four main diagnostic categories, namely uncertainty, anxiety, depressive symptoms and posttraumatic stress. Recommendations will be made for future research.

Method

The following sources of published reviews have been consulted: PubMed, PsychInfo, Cinahl, The Cochrane Library and Web of Science. We prepared search filters and consulted databases to be accessed. The computer databases PubMed, PsychInfo and Cinahl were used for a search with the key words: parent, mother, father, stress reaction, psychological stress, adaptation, coping strategy, neoplasm/ psychology and pediatric cancer. Next, all reference lists of identified papers were examined and then a hand search for identified relevant studies was conducted.

The following criteria for inclusion were applied: firstly, year of publication: studies were published between January 1, 1997, and May 31, 2007, secondly, language: English language studies, thirdly, method: standardized measures of well-documented psychometric quality and the conduct of statistical tests, and lastly, aim: assessment of parental strain, parental stress reactions and the adaptation related to caring for a child with cancer. The following exclusion criteria were applied: case studies, qualitative studies, book chapters, guidelines, commentaries, and dissertations. Reference Manager Version 10 for Windows (Research Information Systems, 2001) was used as the bibliographic software package to organize the relevant references.

Results

We found four other review articles on parental stress, adjustment and coping, first of all the extensive review by Grootenhuis & Last [25] on articles published between 1980 and 1997. A recent review article with a more theoretical character [44] presents an overview of existing literature on the factors influencing parental health and well-being and a review by Bruce [12] has focused on posttraumatic stress in both childhood cancer survivors and their parents. Lastly, Peterson, Cant and Drotar [64] published a review article on the family impact of neurodevelopmental late effects in pediatric cancer survivors. Although there are overlapping issues discussed in our review article and the abovementioned reviews, we also see differences between the articles concerning aims and scope. The present review could be seen as a follow-up on the work done by Grootenhuis and Last [25], concerning articles published in the last ten years, that is between January 1st, 1997, and May 31st, 2007.

We found 79 articles with our search strategy, of which 67 articles met the inclusion criteria. Selected studies are summarized, in chronological order, in Table 1. Studies referring to the same sample are described together. The studies reported in this review are difficult to compare, because they do not only differ in design, but also in sample (both size and heterogeneity), inclusion of control groups, time of assessment, definition of core elements of psychological stress, and measurements.

Methodological issues

Terms used to describe the core elements of parental psychological stress vary considerably between the studies: from emotional strain or psychosocial difficulties to care-giving demands, from affective responses and psychological symptoms to uncertainty, anxiety, depression and posttraumatic stress disorder (PTSD), and from distress, well being and mental health to psychosocial functioning and adjustment.

One time, cross-sectional surveys were employed in the majority of studies. Although these designs are not appropriate to assess the effect of time since diagnosis, they have been used very frequently to assess parental strain in relation to disease phase. Sixteen studies (23% of the total) employed longitudinal designs in order to assess parental manifestations of strain in relation to disease phase. Six intervention studies were included, one of which employed a case control design [41] and five were randomized controlled trials (RCT) [28,34,40,71,72]. The intervention studies will not be further discussed in this review article, because this has been done in a recent meta-analysis by Pai and colleagues [62].

Sample sizes ranged considerably from 15 to 544 parents in cross-sectional studies, from 21 to 164 parents in longitudinal studies and from 18 to 252 parents in the intervention studies. While the majority of studies included both mothers and fathers, twelve studies focused solely on the mothers and two studies [55] included fathers only. Results were compared with control groups, norm groups of the measures and groups of parents of children with other illnesses.

The majority of studies used heterogeneous samples, that is, parents of children with mixed cancer diagnoses. Among the various cancer diagnoses, treatment course varies considerably, with an ensuing risk for complications such as required hospitalizations for chemotherapy, unanticipated hospitalizations for fever and/or neutropenia and varying foci for radiotherapy treatment. These treatment-related events can have a different impact on parental stress. A number of studies did focus exclusively on parents of children with leukemia [7,32,35,48]or a brain tumor [9,19].

In 26 studies parents of children who had recently been diagnosed with of cancer were included, ranging from 1 week to 6 months post diagnosis. Furthermore, 24 studies assessed parents of children in active and/or maintenance treatment, 24 studies assessed parents of children both in- and off treatment, and 26 studies solely included parents of children off active cancer therapy, that is parents of survivors. The definition of survivorship varied considerably between studies. Some researchers considered the number of months and/or years since completion of cancer treatment to be indicative of survivorhood, while others used the number of months and/ or years since diagnosis to

indicate survivorhood. Survivors ranged from 6 months to 10 years since completion of cancer treatment and from 15 months to 13 years since the diagnosis of cancer.

Although it is often concluded that traditional measures of psychopathology may be ineffective and/or insufficiently sensitive in the assessment of psychologically 'healthy' parents in an abnormal crisis situation [6], a substantial body of research still depends on these instruments. This is also true for the studies included in this review.

However, a number of pediatric psychologists have developed and used promising disease-related measures (e.g. [22,26,54,80] and disease-specific measures [9,38,39,52] to assess parental stress reactions related to childhood illness or specifically, childhood cancer. In the majority of studies, these newly developed instruments were used alongside traditional measures on anxiety, depression, PTSS and uncertainty.

Time of assessment of parents of children with cancer ranged considerably between studies. Timing in the cross-sectional studies ranged from diagnosis to more than 7 years post-treatment. In the longitudinal studies, first assessment of parents ranged from one week post cancer diagnosis to more than 5 years post cancer diagnosis.

Emotional Manifestations of Strain According to Disease Phase

Several salient themes appear when examining emotional strain by phase of disease; these include the proportion of parents reporting strain, the correlates of stress reactions and the evolution of these reactions in time. Phases that are distinguished are the diagnostic or consolidation phase, the initial treatment phase, the active treatment phase, the maintenance phase and survivorhood. We will discuss these phases for each diagnostic category.

Uncertainty

Broadly defined, parental uncertainty in childhood cancer pertains to both acute and ongoing or pervasive fear of possible disease consequences like relapse or death [78]. In six studies, all cross-sectional, the construct of uncertainty in childhood cancer was investigated [8,19,25,55,56,73]. Uncertainty in parents of children with cancer has not been compared to uncertainty levels in parents of healthy children.

Compared to parents 1- to 5 years post-treatment, parents of children immediately after completion of treatment reported the most feelings of uncertainty [77]. Between 66% and 90% of parents reported feelings of uncertainty after termination of treatment [8]. Some parents of childhood cancer survivors may continue to be uncertain about the well being of their children many years after the cessation of treatment [25]. In the short term, high levels of uncertainty may interfere with making health decisions. In the longer term, when parental uncertainty becomes chronic, pervading the disease trajectory, it can lead to the development of posttraumatic stress symptoms [53].

Anxiety

Anxiety refers to a complex combination of emotions that include fear, apprehension, and worry. Since anxiety entails an expectation of diffuse and uncertain threat, it plays an obvious role in the experience of parents when confronted with the life-threatening diagnosis of cancer in their child. Approximately 22 studies included in this review investigated the construct of anxiety, of which 13 studies employed a cross-sectional design, 5 studies a longitudinal or prospective design, and 4 studies a RCT or case control design (see Table 1).

Anxiety occurs most frequently around the time of diagnosis and decreases over time. Parents of children newly diagnosed or in active cancer therapy reported higher levels of anxiety than parents of children off active cancer therapy, in remission, or parents whose child has relapsed [54,73,87]. In turn, parents of children with a relapse reported higher anxiety levels than parents of surviving or deceased children [86].

Longitudinal designs show that anxiety levels at diagnosis decrease across time to (near) normal levels five years post diagnosis [85,86]. Yet, symptoms of anxiety seem more common among parents of children with cancer, compared to parents of healthy children, even up to 5 years post diagnosis. This suggests that feelings of anxiety are maintained over time with a subset of parents continuing to be anxious. Prospective longitudinal research has shown that highly anxious parents are at risk for the development of posttraumatic stress symptoms [7,30]. Psychosocial functioning at six months after diagnosis seemed to predict later psychosocial functioning best [86].

Depressive Symptoms

Parents may react to the diagnosis of cancer in their children with depressive symptoms (e.g. [6,59]. Depressive symptoms include, but are not limited to, a persistent sad, anxious or empty mood, feelings of hopelessness or pessimism, feelings of guilt or helplessness, decreased energy, difficulty concentrating or making decisions, restlessness, and insomnia or oversleeping. Twelve studies included in this review investigated the construct of depression, of which 11 studies employed a cross-sectional design, 5 studies a longitudinal or prospective design, and 2 studies a RCT (see Table 1).

High levels of depressive symptoms are reported shortly after diagnosis [2,87]. Mothers of children newly diagnosed, in active cancer therapy and 1-year post diagnosis reported more depressive symptoms than mothers of children off active cancer therapy [84]. Compared to parents of healthy children, parents of children with cancer showed higher levels of depressive symptoms at multiple points from the time since diagnosis [15,59].

In mothers and fathers for whom a longer period of time had elapsed from the time of diagnosis, depressive symptoms were less common [8] but in another study parents consistently reported higher depression scores than the norm group of the questionnaire

under study [29]. Longitudinal studies suggest that depressive symptoms may be maintained over time, especially when parents initially react with moderate to severe levels of depressive symptoms. However, one cannot automatically conclude that the child's diagnosis is the cause of depressive symptoms in parents [57]. Other events, such as marital or financial problems, may also result in depressive symptoms and should be assessed simultaneously. Furthermore, because it is not possible to assess parents prior to the child's cancer diagnosis, the possibility that the depressive symptoms represent a preexisting state cannot be ruled out [51]. Depressive symptoms of the parent may interfere with, for example, health decisions, frequent clinic appointments and the parent-child relationship and communication.

Posttraumatic Stress Symptoms

Learning that one's child has a life-threatening disease is a qualifying event for posttraumatic stress disorder (PTSD) or posttraumatic stress symptoms (PTSS) [3]. Posttraumatic stress acknowledges the life threat inherent in childhood cancer while also providing a framework in which ongoing symptoms such as intrusive thoughts, arousal, and avoidance may be conceptualized and treated [33]. Twenty studies included in this review investigated PTSS or PTSD, of which 13 studies employed a cross-sectional design, 3 studies a longitudinal or prospective design, and 4 studies a RCT or case control design (see Table 1).

Approximately 68% of mothers and 57% of fathers of children currently in treatment report PTSS in the moderate to severe range [37]. Sub-clinical posttraumatic stress symptoms (PTSS) such as intrusive thoughts about cancer, physiological arousal at reminders, and avoidance of treatment-related events have been found to be even more prominent [1]. For parents of childhood cancer survivors the rates of PTSS have been found to range from approximately 10 % [36] to 42 % [19].

Parents of children recently diagnosed or currently in treatment report higher rates of PTSS and current PTSD compared to parents of childhood cancer survivors [33,40,60,66,73]. Mothers and fathers of childhood cancer survivors show significantly higher levels of PTSS and lifetime PTSD than parents of healthy children [5,11,63] but lower than symptom levels for other stressed and traumatized groups [36,43]. An extensive review article on PTSS and PTSD in childhood cancer survivors and their parents has been written by Bruce [12]. He summarized the following risk factors associated with PTSS and PTSD: female gender, greater physical late effects, increased number of prior stressful life events, perceived severity of cancer and treatment, family conflict, poor social support and emotion-focused coping.

It remains a matter of debate whether traumatic stress is a relevant model to describe the emotional reactions of parents of children with cancer [65,82]. However, symptoms of posttraumatic stress (PTS) in parents are a concern and may be an appropriate target for intervention, particularly in the period following diagnosis [66]. Early signs and symptoms of PTS require early assessment and intervention since the disruptive symptoms may linger over time in a subset of parents [4,81].

Emotional Manifestations of Strain and Gender of the Parent

Stress reactions can take different forms in fathers and mothers and it may be relevant to identify these differences in order to deliver specific interventions. Twenty-three studies included in this review compared emotional manifestations of strain in mothers and fathers of children with cancer, of which 13 studies employed a cross-sectional design, 9 studies a longitudinal or prospective design, and 1 study employed a RCT (see Table 1).

Gender Differences in Uncertainty, Anxiety, Depression and PTSS

Evidence for gender differences in parental uncertainty in childhood cancer has not been well established. In one study, mothers of children in remission or with a relapse reported higher levels of uncertainty than fathers [26]. Mothers of children newly diagnosed, in remission, relapsed or off treatment report higher levels of anxiety and depressive symptoms than fathers of children with cancer [32,59,84,86,87], whereas other researchers found no gender differences [18,29]. In one study that focused on fathers who identified themselves as the primary caregiver, elevated rates of depressive symptoms were found more in fathers than mothers [10]. Perhaps being the primary medical caregiver adds to the strain instead of the gender of the parent?

With regard to PTSS and PTSD, mothers have been reported to display more symptoms than fathers [1,12,66,87], especially re-experiencing and arousal symptoms. However, other studies show relatively equal levels of PTSS and rates of current PTSD [33,49,66]. Gender differences in the experience of PTSS may be related to the time of evaluation: over time, only the fathers' symptoms decreased, whereas the mothers' symptoms remained high [49].

In agreement with gender studies on the prevalence of psychological problems in the general population, mothers of children with cancer tend to report more and higher levels of symptoms than fathers. However, it is still not clear whether the differences between mothers and fathers in these studies represent different stress reactions to childhood cancer or are related to general population differences between men and women [76]. Women seem more willing to report discomfort than men. Therefore, gender differences may be due to reporting style [23]. Another explanation may be that mothers more often have the main responsibility for the care of the child with cancer and fathers are more peripherally involved in childcare. The question remains whether it is necessary and possible to tailor interventions to specific needs of mothers and fathers of children with cancer.

Risk factors

Since parents of children with cancer are at risk for the development of disruptive emotional manifestations of strain, which persist over time among a subset of parents, it seems important to obviate risk factors early in order to detect and support parents most at risk for later maladjustment. Several variables have been indicated as risk factors for the development of emotional manifestations of strain.

Risk factors include, but may not be limited to, the following findings: Parents who display the most and highest levels of emotional manifestations of strain at diagnosis continue to experience the highest levels of symptoms, even after treatment ends. Certain demographic characteristics have been identified as risk factors: Parents of children with cancer who are less educated and parents with lower SES [32] or parents with a 'perceived unsatisfactory financial status' [48] report more depressive symptoms.

Trait anxiety has been identified as a predictor of post-treatment PTSS for mothers [7] and for both mothers and fathers [30,43,81]. No association with treatment intensity and minimal associations with time since diagnosis have been found [37]. Child behavior problems [6] were found to be predictive of parental depressive symptoms. High levels of care giving demands, past traumatic life events, and less perceived social support have also been identified as risk factors for the development and maintenance of emotional manifestations of strain.

Attention should be given to parents with pre-existing psychological problems, because they may be less able to deal with the crisis of having a child with a life-threatening disease. Knowledge of risk factors may help identify those parents most in need of psychological care and interventions, preventing these parents from developing disruptive emotional manifestations of strain beyond the 'normal' reactions to the life-threatening diagnosis of cancer.

Protective factors

Several studies have focused on protective factors and on parental adjustment rather than parental stress. We will summarize the positive effect that coping strategies, social support and family relations are shown to have on parental adaptation.

Coping Strategies

Because stressors change with the different phases of cancer, studies on parental coping strategies should be classified according to the phase of cancer [21,83]. Moreover, the adaptive value of a coping strategy is likely to be dependent upon the phase of cancer. Studies addressing changes in coping strategies over the course of childhood cancer are relatively scarce [83]. Avoidance seems to be functional in the early phase of childhood cancer when parents are overwhelmed with stressors. However, in face of active treatment and maintenance, avoidant behavior of the parent has been related to elevated levels of emotional manifestations of strain e.g., anxiety and depression [30,59].

According to Grootenhuis and Last [26], low levels of predictive control coping (i.e. finding it difficult to have positive expectations about the course of the disease), were related to higher levels of emotional manifestations of strain in mothers and fathers of children in remission or with a relapse. More frequent use of active problem focused coping strategies (e.g., acting immediately, being goal oriented), and less frequent use of palliative reactions, avoidance behavior, passive reactions and expressing negative emotions were associated with less depressive symptoms and anxiety in parents of children in active cancer treatment and children that are cancer-free [59].

We recommend longitudinal studies with repeated measures within the same cohort over time to examine which coping strategies are likely to be maladaptive during a particular phase of childhood cancer and require early assessment in order to prevent further psychological problems.

Social Support

Social support seems to have a moderating effect on the impact of anxiety, depressive symptoms and posttraumatic stress symptoms [5,15,18,50,61,76]. Higher levels of perceived social support have been associated with less anxiety [15,59,61,76], lower PTSS levels [5,36]and better adjustment to medical disease [27]. On the other hand, a small network size, more perceived social constraint and a less perceived sense of belonging have been associated with more PTSS in parents of pediatric cancer survivors [7,12,43,76].

Assessing and evaluating both the parent's specific needs for support and the availability of support is important to meet those needs throughout the course of childhood cancer [31].

Family Relations

The family plays an important role in the psychological functioning of both the parents and the child with cancer [5,36,42,69]. Good family relations, adequate family coping and stable family functioning have been reported [36,46,74,75] in studies with a systemic focus. However, marital distress [87], poor family functioning and poor family relationships have been reported as well [80].

Although in most studies family functioning has been investigated as an outcome variable, some studies consider family functioning as a predictor variable for parental adjustment to childhood cancer [25]. Less family cohesion, satisfaction, adaptability and communication have been correlated to parental anxiety and therefore indirectly predicted PTSS [43]. Screening for family functioning, at diagnosis, seems important to identify strengths that can serve as buffers to cope with the stressors to come.

Discussion

The diagnosis and treatment of cancer in one's child can cause long-lasting psychological effects in a parent. Feelings of uncertainty, anxiety, depressive symptoms, and posttraumatic stress symptoms are most prevalent shortly after the parents are confronted with the diagnosis of childhood cancer. These emotional manifestations of strain decrease to near normal levels over time in the majority of the parents, but have been found to persist in a substantial proportion of the parents, even many years post-treatment. Furthermore, as is often found in the general population, mothers tend to report more and higher levels of symptoms than fathers with respect to anxiety, depression and PTSS. These differences may well be related to the traditional distribution of care-giving tasks and responsibilities. Also, since women seem more willing to report discomfort than men, gender differences may also be due to reporting style [23]. The question remains whether these gender differences are meaningful and, consequently, whether mothers require specific intervention efforts.

Assessment of parental stress reactions is important to identify those parents most in need. The following risk factors have been indicated: female gender, pre-existing psychological problems, high trait anxiety, low social economic status and financial worries, child behavior problems, high perceived care-giving demands, and less perceived social support. Certain coping strategies, such as active problem solving seeking, social support and optimism can serve as protective factors. Specific strengths of the family should be identified and used. Parents might well benefit from a tailored intervention based on strengths and weaknesses that is targeted to their specific needs with respect to the phase of childhood cancer [28,30,34,76,80].

In most of the studies included in this review parents of children with heterogeneous diagnoses were assessed, making comparisons difficult. Different rates of uncertainty, anxiety and other stress reactions may be directly associated with the child's type of cancer (e.g. parenting a child with standard risk ALL versus a child with a malignant brain tumor). The inclusion of predominantly white parents and the assessment of either mothers alone or parents as a couple causes bias and generalization problems. The inclusion of non-native speaking parents continues to be a difficulty, although efforts are being made to translate assessment instruments and intervention programs for these groups, e.g. [70,71].

A wide variety of assessment measures to measure parental emotional manifestations is seen across studies. As has been stated by many others, relevant, reliable, and valid assessment tools for parents of children with cancer are critically important in advancing the field of pediatric psychology because they can provide further evidence of the impact of childhood chronic disease on parents, as well as the potential need for and impact of psychological interventions [25,45,79]. However, parents of children with cancer are coping with an abnormal situation and therefore existing instruments may fail to assess their specific problems [25]. This can lead to "pathologizing" parental adaptation to childhood illness, which can have negative effects such as increased stigma and a de-emphasis on parents' daily functioning [67].

Disease-related and disease-specific measures can provide valuable, additional information when administered together with general measures [80]. It would be beneficial to both research and patient care to make use of the strengths of each different type of instrument. Sound psychometric properties of disease-related and disease-specific measures still need to be established and comparison groups are often small. Multi centered research and (inter) national collaboration is needed to obtain larger samples and to validate disease-related and disease-specific questionnaires developed by others or –better yet- to develop new measures together. The DISABKIDS project [13] and the KIDSCREEN project [68] are excellent examples of successful international collaborative projects yielding valid and reliable assessment tools to measure health related quality of life in children with chronic conditions. Unfortunately oncology was not incorporated in these projects.

Looking back on the last ten years in pediatric psycho-oncology research, there is a trend toward larger studies; almost half (32) of the studies included at least 100 parents (in most cases both mothers and fathers were included). The proportion of longitudinal studies seems to rise somewhat (14 % in the Grootenhuis & Last review versus 23% in the present review), but the majority of designs is still cross-sectional. This seems somewhat surprising, because in almost all articles the necessity of longitudinal designs is argued.

Recommendations

The present review study reveals potential areas of improvement in future research. In the 67 studies included in this review a variety of definitions of the core elements of the psychological stress process have been used, often described together and simply referred to as 'stress'. It is important to clarify what is meant by 'stress' and to specify the temporal course of a stressor [45]. To facilitate communication and collaboration it is necessary to be more specific in the terminology used to describe the psychological reactions of both parents and patients, and to make a clear distinction between stress as a primary reaction and psychological stress as an outcome. Investigators must determine whether they are interested in the person's appraisal of the stressors, or simply in the occurrence of verifiable events. Another issue is the temporal course of the illness or condition itself, since the phase of an illness guides the 'timing' of the assessment [16]. These aspects need to be specified before proceeding further with the study design and measurement strategy. In many instances, it matters whether the investigator is interested in processes that occur at the time of disease onset, in the period following initial diagnosis, during the

course of treatment, when complications arise (such as a relapse) or in the longer term.
It seems we have no more need of more cross-sectional research in this area, given its limitations. Repeated, ongoing assessment with longer time frames remains necessary to follow parents prospectively through the different phases of illness, treatment and long-term survival. It is recommended that a consensus be established on the optimal points in time to assess emotional reactions in parents following the diagnosis of cancer in their child. If assessments would take place for example one, six and 12 months after diagnosis, at the end of treatment and one and/or two years after the cessation of treatment, the comparison of results from research would be facilitated and patient and parent care would be enhanced. Assessment shortly after diagnosis provides important information on the initial reactions of parents. However, clinical practice has shown that assessment within four weeks after diagnosis is difficult, because parents are often too overwhelmed to take the time to fill in questionnaires. Assessment at six and twelve months post diagnosis will give insight in parental stress over time according to different disease phases. The end of treatment brings new challenges for parents and longer term follow-up is necessary to keep track of the parents who still report high stress levels.
After identifying those parents most in need of more intensive psychological care, the next step is to deliver feasible, limited, brief interventions for sub-clinical manifestations of psychological distress. Intervention research is a growing area in pediatric psychology and despite the many methodological challenges; efforts should be made to implement and evaluate existing intervention programs to prove effectiveness. This can only be done through (inter)national cooperation and well-developed study designs.
Furthermore, it is recommended that investigators routinely describe their reasons for using particular assessment tools or questionnaires, which should be embedded in an underlying theoretical model. Researchers seldom document their arguments for the selection of assessment measures used in their studies. This is unfortunate, because it would give more insight in the underlying theoretical model and it could facilitate discussion and communication among peers. One should also consider that measures could be used for different purposes. Important questions are: What does this measure do best? Is it a screening tool? Is it able to establish a diagnosis or to obtain a detailed picture of the problem? Is suitable for evaluating treatment outcome? [45]. Method and measure should match the study's purpose. A screening instrument is not intended to analyze a person, but to direct scarce professional time to cases meriting more in-depth study or support [14]. Development of brief screening instruments is important to identify parents at risk for preexisting, ongoing and escalating emotional manifestations of strain [39].
Lastly, instead of 'pathologizing' parents by classifying them as anxious or depressed [67], it would be more helpful to investigate parents' quality of life. Parental adjustment to childhood illness should be considered as a normative process involving additional daily responsibilities, limitations in major life roles and increased strain in close relationships. What is asked of parents is much more than in a normal parenting situation and acknowledging this would help parents cope better with the difficult and stressful situations with which they are confronted.

Table 1. Summary of Studies assessing Parental Psychological Stress in Childhood Cancer, in Chronological Order

Reference Design	Aim	Parent (n)	Child Characteristics	Parent Measures	Findings
Allen et al., 1997 [47] Cross Sectional	Investigate the impact of cancer diagnosis on psychological wellbeing of children and parents	34 M 27 F	Mixed diagnoses Median time post diagnosis 3 weeks	STAI BDI	Parental anxiety was higher than norms. M were most anxious. There were no gender differences found in depression
Barakat et al., 1997 [48] Cross Sectional	Compare PTSS in cancer survivors and parents with healthy children and parents	309 M 213 F	Mixed diagnoses Survivors Mean yr off treatment 5.8	PTSD-RI STAI IES FACES ALTTIQ SNRDAT	M and F had higher levels of PTSS than controls. Past perceived life threat and social support were contributors to PTSS
Grootenhuis & Last, 1997b [49] Cross Sectional	Determine which variables predict emotional adjustment of parents	84 M 79 F	Mixed diagnoses In & off treatment Mean mo post diagnosis: 51 1. Remission 54 2. Relapse 47	BDI TRAIT SSERQ CSS	A lack of positive expectations about the course of the illness was most strongly related to negative emotions. Having a child with a relapse predicted helplessness and uncertainty for M. Depression in the child was related to uncertainty of the father
Kazak et al., a. 1997 [29] b. 1998 [30] Cross Sectional	a. Examine psychological sequalae survivors and their parents compared to healthy controls b. Compare symptoms of anxiety and PTSS	a-b. 130 M 96 F	a-b. ALL & ANLL Survivors Mean yr off treatment 5.8	a. FACES SNRDAT a-b. IES STAI PTSD-RI	a. No differences in family functioning and social support a-b. More PTSS in M and F of survivors
Moore & Mosher, 1997 [50] Cross sectional	Examine adjustment responses of mothers and children (self care and anxiety) to cancer	74 M	Mixed diagnoses In & off treatment	STAI DCAPQ	M of children off treatment showed better adjustment responses than M of children in treatment. Basic conditioning factors predict adjustment responses. A relationship between mother/child adjustment was found
Sawyer et al., a. 1997 [51] b. 1998 [52] c. 2000 [53] Longitudinal	a. Follow prospectively adjustment of children and parents first 2 years post diagnosis b. Examine relation parent and family adjustment post diagnosis and adjustment of the child 2 yr post c. Assess psychological adjustment of children treated for cancer and their parents	a-b. 38 M 31 F c. 39 M 31 F	a-b-c Mixed diagnoses In & off treatment T1: mean weeks post diagnosis 5 a. T2: 1 & 2 yr post T1 b. T2: 2 yr post T1 c. T2-T5: 1, 2, 3 and 4 yr post T1	a-b-c FAD-GFS GHQ	a. Children and parents reported more emotional distress than controls post diagnosis. N of problems declined the first year and stabilized at comparable level with controls b. Distress level M post diagnosis were potential important influence on child adjustment c. Parents and children reported more psychological problems than controls post diagnosis. In the longer term, there were no differences in the number of problems
Hoekstra-Weebers et al., 1998 [24] RCT	Evaluate psycho educational intervention program parents of children with cancer	20 M 19 F	Mixed diagnoses In treatment T1: ≤ 14 days, T2: 6 and T3: 12 mo post diagnosis	STAI-State SCL90 SSL-D GHQ-12 Intensity Emotions List	Although there was a positive clinical evaluation, the structured intervention program was no more effective than standard care
Hoekstra-Weebers et al., a. 1998 [54] b. 1999 [55] c. 2001 [56] Wijnberg-Williams et al., d. 2006 [57] e. 2006 [58] Prospective	a. Examine gender differences in adaptation to diagnosis, and relation with coping style of parents of children with cancer b. Examine risk variables for future, immediate and persistent psychological distress parents c. Investigate level support and concurrent, prospective effects support on functioning parents d. Explore effects social support on psychological distress of parents of pediatric cancer patients e. Examine change and gender differences in self reported distress	a-b-c. T1: 85 M 79 F T2-T3: 66 M 62 F d-e. T4: 58 M 57 F	a-b-c. Mixed diagnoses In treatment T1: ≤ 14 days, T2: 6 and T3: 12 mo post diagnosis d-e. Survivors Deceased T4: 5 yr post diagnosis	a. SCL90 b. STAI-Trait SIB QREE RSES a-b. UCL a-b-c-d-e. GHQ-12 b-c-d. SSL-I SSL-D e. SCL90 STAI-State	a. More psychiatric symptoms and psychological distress at diagnosis, no gender differences. Distress declined with time. Few gender differences coping b. Trait anxiety was the strongest predictor of distress. Social support additional risk factor F. Previous life events and assertive behavior additional risk factors M c. Most support at diagnosis. Decrease of support with time but parents were equally satisfied. Dissatisfaction with social support and negative interaction was a risk factor for F, not M. Well adjusted M got more support than M who remained clinically distressed d. Decreased distress and support T1-T4. No change in satisfaction support and negative interaction. Dissatisfaction with support and negative interactions affected distress F, not M e. Decreased distress, psycho-neurotic symptoms and anxiety to normal level T4, except on GHQ. M more anxiety than F. Parents of children who relapsed reported more anxiety than parents of survivors or deceased children
Kazak et al., 1998 [30] Cross Sectional	Predict PTSS in parents of childhood cancer survivors	320 M 224 F	Mixed diagnoses Survivors Mean yr off treatment 5.7	PTSD-RI STAI FACES SNRDAT ALTTIQ	Anxiety was the strongest predictor of PTSS. Other contributors were: perceived life threat, treatment intensity and social support
Kazak et al., 1999 [20] Case control	Piloting Surviving Cancer Competently Intervention Program (SCCIP). Evaluate changes in PTSS, anxiety and family functioning	19 M 13 F	Mixed diagnoses Survivors Off treatment	PTSD-RI IES STAI-State FLS	PTSS and anxiety decreased in the participants. Changes in family functioning were difficult to discern

Reference Design	Aim	Parent (n)	Child Characteristics	Parent Measures	Findings
Barakat et al., 2000 [59] Longitudinal	Explore impact PTSS on long- term, psychological functioning of cancer survivors and M	65 M	Mixed diagnoses Survivors T1: Mean mo off treatment 58 T2: 18 months post T1	T1: PTSD-RI IES ALLTIQ T2: BSI LES	PTSS at T1 predicted general adjustment at T2, approximately 18 months later
Dockerty et al., 2000 [60] Cross Sectional	Assess mental health parents of children with cancer, compared to healthy controls	218 M 179 F	Mixed diagnoses In treatment	GHQ-12 VAS CAGE LTE-Q B-SSQ	Significant but small differences in mental health M and F of children with cancer compared to controls. Parents of children with cancer are relatively resilient
Manne et al., 2000 [61] Cross Sectional	Investigate individual differences in coping style, lifetime traumatic events, social support and PTSS	72 M	Mixed diagnoses Survivors Mean yr off treatment 2.5	PCL-C ISEL MBSS LEC	13.5 % of the M had symptoms indicative of cancer related PTSS Perceived social constraints and 'lack of belonging' were associated with PTSS.
Sloper, 2000 [62] Longitudinal	Investigate psychological distress in parents and relations between illness variables, appraisal, psychosocial resources and coping strategies	68 M 58 F	Mixed diagnoses In & off treatment T1: 6 mo and T2: 18 mo post diagnosis	T1-T2: MI T1: FES SSRM-SNSS BLCS WCQ	51% M and 40% F reported high distress levels at T1 and T2. M: Appraisal of strain, ability to deal, more self-directed coping and family cohesion were predictive of distress. F: risk employment problems, number of hospitalizations, appraisal and family cohesion were predictive of distress
Best et al., 2001 [31] Longitudinal	Evaluate association parental anxiety during treatment childhood leukemia and PTSS post treatment	66 M 47 F	ALL & AML T1: In treatment T2: Mean yr off post T1 3.7	T1: PPQ T2: STAI-State PAAS IES-R PTGI SNRDAT	Anxiety during treatment was a predictor of PTSS for M, not F. Anxiety, self-efficacy, posttraumatic growth and time since treatment were associated with avoidance
Frank et al., 2001 [63] Cross Sectional	Determine whether cognitive appraisals, perceptions of child behavior and social support predict affective responses differentially for M and F	77 M 48 F	Mixed diagnoses In & off treatment Mean yr post diagnosis: M: 2.7 and F: 2	BDI STAI ASQ CHIP	Parents did not differ on any of the variables. There were differential predictors of affective responses for mothers and fathers
Fuemmeler et al., 2001 [33] Cross Sectional	Examine PTSS and general distress among parents of children with a brain tumor	18 M 10 F	Brain tumor Off treatment Mean yr post diagnosis 6.8	PDS BSI PPUS WCQ	Parents of survivors of brain tumor were found to be at risk for PTSS and general distress. Uncertainty in illness was a primary risk factor for adjustment problems
Goldbeck, 2001 Longitudinal [64]	Study effect coping dissimilarity within couples on QoL of parents of children with cancer, compared to parents of children with diabetes or epilepsy	25 M 25 F	Mixed diagnoses In treatment Mean weeks post diagnosis: T1: 1-2 T2: 8-12	ULQIE CHIP TCS	Parents of children with cancer used more rumination, defense, information seeking, and less social support seeking than controls. M more frequent and effective coping strategies than F, but no differences in QoL. Coping dissimilarity F and M has a differential effect on family members

Reference Design	Aim	Parent (n)	Child Characteristics	Parent Measures	Findings
Mu et al., 2001 Cross Sectional [65]	Examine impact of stress experienced by M during cancer treatment of the child	100 M	Mixed diagnoses In treatment Mean length of treatment 12 mo	STAI-State PPUS BAS SMS	Sense of mastery was a mediator for uncertainty and anxiety. Uncertainty was a good predictor for boundary ambiguity
Iqbal & Siddiqui, 2002 [32] Cross Sectional	Determine frequency of depression in parents of children with ALL	37 M 23 F	ALL Off treatment First remission within last month	SCID-IV MMSE	Depression found in 34 parents, more common among M, less educated parents, lower SES
Goldenberg-Libov et al., 2002 [66] Cross Sectional	Examine prevalence and predictive factors of PTSD and PTSS in M	49 M	Mixed diagnoses Survivors Off treatment	SCID-PTSD PSEI	20 % M current and 27 % M lifetime PTSD. The number of low magnitude stressors past year, the perception of the cancer threat and income were contributors to the prediction of PTSS
Mu et al., 2002 [67] Cross Sectional	Examine stress impact on F caring for children undergoing cancer treatment	76 F	Mixed diagnoses In treatment Mean weeks in treatment 15	STAI-State PPUS PMS	Uncertainty and level of education were good predictors of anxiety
Sahler et al., 2002 [21] Two-arm RCT	Examine feasibility and effects Problem Solving Skills Therapy (PSST) with M of newly diagnosed children	50 M	Mixed diagnoses In treatment Mean weeks from diagnosis to T1: PSST 8.9 Controls 9.3	POMS SPSI-C	M in PSST-intervention condition showed enhanced problem-solving skills and decreased negative affectivity compared to controls
Santacroce, 2002 [68] Cross Sectional	Describe relations between uncertainty, anxiety and PTSS in parents	12 M 3 F	Mixed diagnoses In treatment Mean weeks post diagnosis 5	STAI-State PTSD-RI PPUS	Level of uncertainty was lower than expected. Anxiety level was comparable to hospitalized persons with anxiety disorders. Level of PTSS was higher than parents of survivors. There was a significant relation between anxiety and PTSS
Yeh, 2002 [69] Cross sectional	Investigate gender differences stress in parents of C with cancer diagnosis	164 M 164 F 1. 48 M & F 2. 43 M & F 3. 23 M & F 4. 47 M & F	Mixed diagnoses In & off treatment 1. Diagnosis ≤ 2 mo 2. In remission 3. Relapse 4. Off treatment	PSI-SF MSS SCL35-R	M reported higher distress levels than F. Parents of children newly diagnosed with cancer showed higher levels of depression, anxiety, stress and marital dissatisfaction
Boman et al., a. 2003 [70] b. 2004 [71] Cross Sectional	a. Understand reactions M and F of children with cancer b. Compare incidence disease- related distress symptoms in M and F of children with cancer and parents of children with diabetes	a-b. 146 M 118 F	a-b. Mixed diagnoses In & off treatment Mean mo post diagnosis 34	a-b. PPD-C	a. Distress levels (loss control, self-esteem, anxiety, depression, sleep disturbance, psychological and physical distress) were lower with more time elapsed since diagnosis b. Parents of children with cancer reported higher levels of anxiety, depression, loneliness, psychological and physical distress than parents of children with diabetes

Reference Design	Aim	Parent (n)	Child Characteristics	Parent Measures	Findings
Brown et al., 2003 [72] Cross Sectional	Examine adjustment among cancer survivors and M. Determine differences in PTSS relative to healthy comparisons	52 M	Mixed diagnoses Survivors Mean yr off treatment 5	PTSD-RI FILE FES	M of children with cancer reported more PTSS and more recent and past stressful life events than controls
Han, 2003 [73] Cross Sectional	Identify factors that influence maternal psychosocial adjustment to childhood cancer	200 M	Mixed diagnoses In treatment Relapse	FILE PAIS VAS CHIP PRQ	Stress, coping, social support and time since diagnosis significant were correlates of maternal psychosocial adjustment
Kazak et al., 2003 [74] Prospective	Identify risk level for psychosocial distress in families of children newly diagnosed cancer	103 M 15 F 2 Grand mothers	Mixed diagnoses In treatment T1: Mean days post diagnosis 9 T2: Mean mo post diagnosis 4	PAT	The PAT identified three subsets of families with increasing psychosocial distress at diagnosis
Steele et al., a. 2003 [75] b. 2004 [76] Longitudinal	a. Examine maternal distress initial 6 mo post diagnosis, and relation between changes distress and parenting strategies b. Identify distress patterns initial 6 months and examine patterns as predictors of child distress	a-b 65 M	a-b Mixed diagnoses In treatment Mean weeks post diagnosis: T1: 2-5 T2: 12-14 T3: 22-24	a-b. PSI POMS-SF a. CBS PDI b. PSS	a. The perceived and affective distress M decreased. Consistency of parenting fluctuated. Other parenting strategies and caregiver burden remained stable b. Four patterns of maternal distress. The high maternal stress group reported higher emotional distress in their child at T1, 2 and higher somatic distress at T3
Streisand et al., 2003 [77] Cross Sectional	Examine relation pediatric parenting stress and family functioning	96 M 20 F	Mixed diagnoses In/off treatment Mean mo post diagnosis 38	PIP FAD	Increased pediatric parenting stress is associated with poorer family functioning outcomes
Trask et al., 2003 [78] Cross sectional	Examine relations distress, coping, social support and family adaptation within pediatric cancer population and parents	28 M 1 F	Mixed diagnoses In/off treatment Mean mo post diagnosis 18	BSI FACES CSI	Low-level distress was reported, with a positive relation between parent-child adjustment. More use of adaptive coping strategies. Distress was associated with a reduced use of adaptive strategies
Barrera et al., 2004 [79] Cross Sectional	Determine if cancer diagnosis brings unique adjustment challenges	69 M	Mixed diagnoses In treatment Diagnosis ≤ 3 weeks	BDI STAI SCL90-R: GSI FIRA-G WCQ	M of children with cancer reported more depressive symptoms, emotion focused coping, and social support than controls. M of children with cancer had more adjustment difficulties uniquely related to child behavior
Von Essen et al., 2004 [80] Cross Sectional	Investigate well-being and burden of symptoms among parents of children with cancer	118 M 83 F	Mixed diagnoses In & off treatment Diagnosis within one mo	GQOLI	F had a higher mental wellbeing. M reported more symptoms of depression. Parents in treatment reported lower social and mental wellbeing and more depressive symptoms than parents off treatment
Hung et al., 2004 [81] Cross Sectional	Evaluate whether stress differs between parents of children with physical disability and parents of children with cancer	89 Parents	Mixed diagnoses In treatment Newly diagnosed or relapse	PSI-SF	Parents of children with cancer reported higher levels of stress than parents of children with a physical disability
Kazak et al., 2004 RCT [18]	Evaluate reduction of PTSS related to cancer	146 M 106 F	Mixed diagnoses Survivors 1-10 yr off treatment	IES-R PTSD-RI STAI-State	There were significant reductions in intrusive thoughts among fathers in the experimental group (SCCIP)
Kazak et al., 2004 [19] Cross Sectional	Describe rates and concordance of PTSD and PTSS in adolescent cancer survivors and M and F	146 M 103 F	Mixed diagnoses Survivors Mean yr off treatment 5	IES-R PTSD-RI SCID-PTSD	M and F reported relatively equal rates of PTSS and current PTSD. Nearly 30% M met criteria since diagnosis, with 13% currently In nearly 20% families at least one parent had current PTSD. At least one family member had re-experiencing symptoms
Lähteenmaki et al., 2004 [82] Longitudinal	Evaluate impact of childhood cancer on the life of the parents	21 Parents	Mixed diagnosis In treatment T1: 3 mo and T2: 12 mo post diagnosis	STAI-State Non-standardized questionnaire	In the beginning the high loss income and strain were intolerable. Negative view of own health but positive attitude on family life and spousal relation. Standardized anxiety assessment failed to show increase
Magal-Vardi et al., 2004 [83] Longitudinal	Assess development psychiatric morbidity, evaluate HRQoL and specify traumatic events leading to PTSS	20 M 16 F	Mixed diagnoses In treatment T1: < 2 weeks, T2: 1 mo and T3: 6 mo post hospitalization	DTS	20 % of the parents showed signs of PTSS within the first two weeks after diagnosis. No change in maternal PTSS, a decrease in PTSS in fathers. Several events were identified as causes
Quin, 2004 [84] Cross Sectional	Examine long-term psychosocial effects of cancer on children and families	74 M 46 F	Mixed diagnoses Survivors Off treatment	GHQ COPE	Shortly after treatment: isolation, vulnerability and ongoing worries were reported. Gender differences in coping. Majority of the parents readjust to ordinary family life post treatment
Svavarsdottir, 2004 [85] Longitudinal	Identify time-consuming and difficult care giving tasks experienced by M and F	T1: 25 M 20 F T2: 22 M 18 F T3: 21 M 15 F	Mixed diagnoses In/off treatment Recurrence ≤ 6, ≤ 18, ≤ 24 mo diagnosis- study baseline	CMCCQ GWB	Emotional support was the most time consuming and difficult task for M & F. M: manage behavioral problems and structure-plan family activities. F: manage work-organize care and give emotional support to the partner
Alderfer et al., 2005 [86] Cross Sectional	Identify and describe potential PTSS patterns within couples	49 M 49 F	Mixed diagnoses Survivors Mean yr off treatment 5.3	PTSD-RI IES-R SCID-PTSD FLS	5 Clusters of PTSS were found. The majority of the families have at least one parent with moderate-severe PTSS

Reference Design	Aim	Parent (n)	Child Characteristics	Parent Measures	Findings
Kazak et al., 2005 [23] RCT	Report initial feasibility and outcome of pilot study SCCIP-Newly Diagnosed	9 M 8 F 1 Grand mother	Mixed diagnoses Newly diagnosed In treatment	T1: ASDS T2: STAI-State IES-R	Reduced anxiety and PTSS after completion of intervention (SCCIP-ND) was reported
Kazak et al., 2005 [87] Cross Sectional	Investigate PTSS in parents of C in treatment and association with treatment intensity and time since diagnosis	119 M 52 F	Mixed diagnoses In treatment Mean mo post diagnosis 15	PTSD-RI IES-R	All but one parent reported PTSS. Mean scores indicated moderate PTSS. Two parent families: 80% at least one parent with moderate-severe PTSS. M and F reported more distress than controls. Minimal associations with time since diagnosis. No association with treatment intensity
Norberg et al., a. 2005 [88] b. 2005 [89] Cross Sectional	a. Consider range of parental coping strategies. Examine relation between coping strategies and anxiety and depression b. Examine relations between anxiety, social support seeking and perceived social support M and F survivors	a. 224 M 171 F b. 103 M 81 F	a-b. Mixed diagnoses a. In treatment a-b. Off treatment b. Survivors	a. ZDS a-b. STAI-State UCL b. Social Support Scale	a. No difference in the frequency of coping strategies. More active problem focusing, less avoidance and passive reaction were related to lower levels of anxiety and depression. Contextual demands influence relation coping-anxiety-depression b. A positive relation between support seeking and perceived support was found. Negative relation between anxiety and support seeking, stronger for M than F
Norberg et al., 2005 [90] Cross Sectional	Investigate traumatic stress in parents of children in active treatment versus off treatment	230 M 183 F	Mixed diagnoses In & off treatment Mean mo post diagnosis 19	IES-R	More intrusion and arousal parents of children in treatment. No difference between parents of children with and without a relapse. Post treatment: being immigrant and less educated, higher risk elevated stress. M more stress than F
Phipps et al., a. 2005 [91] b. 2006 [92] Cross Sectional	a. Examine PTSS levels in children and parents as a function of time elapsed post diagnosis and by use of parent versus child report for assessing patient PTSS b. Examine levels PTSS in children with cancer and their parents as function of adaptive style	a. 1. 35 Parents 2. 34 Parents 3. 30 Parents b. 99 M 18 F 4 Step- or Grandparents	a-b. Mixed diagnoses 1. In treatment, ≥ 2-≤ 6 mo post diagnosis 2. In/off treatment, 18-30 mo post diagnosis 3. Off treatment, ≥ 5 yr post diagnosis 4. Off treatment, ≥ 5 yr post diagnosis and age ≥ 18	a-b. IES-R PTSD-RI b. WAI	a. Parents of children recently diagnosed reported higher PTSS levels than parents of survivors. b. Low anxious and repressive parents reported lower PTSS levels than high anxious parents

Reference Design	Aim	Parent (n)	Child Characteristics	Parent Measures	Findings
Sahler et al., 2005 [22] RCT	Replicate PSST with larger and more diverse sample. Test Spanish version and examine moderators effectiveness PSST	217 M	Mixed diagnoses In treatment Mean weeks to randomization: 9	POMS BDI-II IES-R NEO-FFI SPSI-R	M in PSST showed enhanced problem-solving skills and decreased negative affect compared to controls. Effects were largest immediately after training
Stam et al., 2005 [93] Cross Sectional	Investigate HRQoL of children and emotional reactions of parents shortly after treatment	124 M 111 F	Mixed diagnoses Mean mo off treatment 2	GHQ-30 SSERQ	Parents of children with cancer reported more psychological distress than norms. More loneliness, helplessness and uncertainty was reported than parents of children 1-5 yr post cancer treatment
Barakat et al. [94], 2006 Cross-sectional	Describe posttraumatic growth (PTG) and its association with various variables	146 M 107 F	Mixed diagnoses Mean years off treatment: 5,3	PCS-scale from ITSIS ALTTIQ IES-R	A majority of the parents and adolescents in the study reported PTG. Greater perceived treatment severity and life threat was associated with PTG.
Bonner et al. [95], 2006 Cross-sectional	Develop a disease related measure of parent adjustment : PECI	157 M 38 F 7 grandm.	Brain tumors In/off treatment	BSI CGSQ IES IFS PECI	The PECI was proven to be reliable and valid. Four factors emerged: Guilt and Worry, Emotional Resources, Unresolved Sorrow and Anger and Long-term Uncertainty.
Lou, 2006 [96] Cross-sectional	Exploring factors related to the psychological wellbeing of parents of children with cancer	23 M 7 F 1 grandf	Leukemia In treatment, 1-44 mo since diagnosis (M 9.6)	PCI, GHQ	Parents are at risk for poor psychological well being related to financial problems and a lack of self-oriented coping approaches
Norberg et al., 2006 [97] Cross-sectional	Examine relationships between anxiety, seeking social support and perceived social support	103 M 81 F	Mixed diagnoses Off treatment	UCL STAI PPUS	Parent's subjectively perceived support appears to be more important for anxiety regulation than their support-seeking coping.
Phipps et al., 2006 [98] Cross-sectional	To examine symptom levels of PTS in children with cancer and their parents as a function of patient and parent adaptive style	99 M 18 F 4 other	Mixed diagnoses In/off treatment	IES-R, WAI	Parents identified as low anxious or repressors self-reported lower levels of posttraumatic stress (PTS) than high anxious parents. They also reported lower levels of PTS in their children
Bonner et al., 2007 [99] Cross-sectional	Evaluate the psychosocial functioning of fathers as primary caregivers of pediatric oncology patients	23 F 23 M	Mixed diagnoses In/off treatment	BSI IES IFS CGSQ PECI	The majority of parents were above normative means on measures of psychological distress. A large proportion of fathers reported elevated levels of depression
Robinson et al., 2007 [100] Cross-sectional	Identify factors that influence the association between parent and child distress	94 M 67 F	Mixed diagnoses In treatment	SCL-90 R FES NNSI CBCL	Children whose parents were distressed were more likely to be distressed . Subgroups of children were found to be more vulnerable to the father's distress

Note. ALL, Acute Lymphocytic Leukemia; ALTTIQ, Assessment of Life Threat and Treatment Intensity Questionnaire; AML, Acute Mylogenic Leukemia; ANLL, Acute Nonlymphoblastic Leukemia; ASDS, Acute Stress Disorder Scale; ASQ, Attributional Style Questionnaire; BAS, Boundary Ambiguity Scale; BDI, Beck Depression Inventory; BSI, Brief Symptom Inventory; BLCS, Brief Locus of Control Scale; B-SSQ, Brief Social Support Questionnaire; C, Child (ren); CAGE-Q, Screening test alcohol abuse; CARS, Current Adjustment Rating Scale; CBS, Caregiver Burden Scale; CES-D, Center for Epidemiological Studies Depression Scale; CGSQ, Caregiver Strain Questionnaire; CHIP, Coping Health Inventory for Parents; CMCCQ, Care of My Child with Cancer Questionnaire; COPE, Coping-scale; CSI, Coping Strategies Inventory; CSS, Control Strategy Scale; DAS, Dyadic Adjustment Scale; DCAPQ, Dependent Care Agent Performance Questionnaire; DTS, Davidson Trauma Scale; F, Father; FACES, Family Adaptability and Cohesion Evaluation Scale; FAD, Family Assessment Device; FCS, Family Coping Scale; FES, Family Environment Scale; FILE, Family Inventory of Life Events Environment and Change; FIRA-G, Family Index of Regenerativity and Adaptation-General; FLS, Family Life Scales; FRI, Family Routines Inventory; GHQ, General Health Questionnaire; GSI, Global Severity Index; GWB, General Well-Being Schedule; GQOLI, Göteborg Quality of Life Instrument; HDRS, Hamilton Depression Rating Scale; HRQoL, Health Related Quality of Life; IES, Impact of Event Scale; IOFS, Impact on Family Scale; ISEL, Interpersonal Support Evaluation List; IRSS, Illness Related Social Support Scale; ITSIS, Impact of Traumatic Stressorts Interview Schedule; JCS, Jalowiec Coping Scale; LEC, Life Events Checklist; LES, Life Experience Survey; LTE-Q, List of Threatening Experiences Questionnaire; LWMA, Locke Wallace Marital Adjustment Scale; M, Mother; MBSS, Miller Behavioral Style Scale; MI, Malaise Inventory; MMSE, Mini Mental State Examination; MQ-OS, Marital Questionnaire-Overall Satisfaction Scale; MSS, Marital Satisfaction Scale; N, Number; NEO-FFI, NEO-Five Factor Inventory; N.o.s., Not otherwise specified; NSSI, Norbeck Social Support Questionnaire; PAAS, Pediatric Anxiety and Avoidance Scale; PAIS, Psychosocial Adjustment to Illness Scale; PAT, Psychosocial Assessment Tool; PCI Parenal Coping Inventory; PCL-C, Post-traumatic Symptom Disorder Checklist-Civilian Version; PDI, Parenting Dimensions Inventory; PDS, Posttraumatic Stress Diagnostic Scale; PGIHQ, Patient Generated Index Health Questionnaire; PIP, Pediatric Parenting Stress; PMS, Pearlin Mastery Scale; POMS, Profile of Mood Scale; PPQ, Perception of Procedures Questionnaire; PPD-C, Parental Psychological Distress in Childhood Cancer; PPIS, Parental Perception of Illness Severity scale; PPUS, Parent's Perception Uncertainty in Illness Scale; PRQ, Personal Resource Questionnaire; PSEI, Potential Stressful Events Interview; PSI, Parenting Stress Index; PSR, Provisions of Social Relations; PSS, Perceived Stress Scale; PSST, Problem-Solving Skills Training; PTGI, Post Traumatic Growth Inventory; PTSSD-RI, Posttraumatic Stress Disorder Reaction Index; QoL, Quality of Life; QREE, Questionnaire of Recently Experienced Events; RCT, Randomized Controlled Trial; RS, Modified Repression-Sensitization Scale; RSES, Rosenberg Self-Esteem Scale; SCCIP (-ND), Surviving Cancer Competently Program (-Newly Diagnosed); SCID-PTSD, Structural Clinical Interview for DSM-IV Section Posttraumatic Stress Disorder; SCL90-R, Symptoms Checklist-90-Revised; SES, Socioeconomic Status; SIB, Scale for Interpersonal Behavior; SMS, Sense of Mastery Scale; SNRDAT, Social Network Reciprocity and Dimensionality Assessment Tool; SRRS, Social Readjustment Rating Scale; SSQ, Social Support Questionnaire; SSL-D, Social Support List Interactions; SSL-I, Social Support List Discrepancies; STAI, Spielberger's State Trait Anxiety Inventory; SPSI-C, Social Problem-Solving Inventory-Cancer; SPSI-R, Social Problem-Solving Inventory-R; SSERQ, Situation Specific Emotional Reaction Questionnaire; SSRM-SNSS, Social Support Resources Measure-Support Network Satisfaction Scale; TRAIT, Dutch version Trait Anxiety Inventory; TCS, Trier Coping Scales; UCL, Utrecht Coping List; ULQIE, Ulm Quality of Life Inventory for Parents of a Chronically Ill Child; VAS, Visual Analogue Scales; WAI, Weinberger Adjustment Inventory; WCQ, Ways of Coping Questionnaire; yr, year

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Psychometric qualities of the Dutch version of the Pediatric Inventory for Parents (PIP): a multi-center study

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Abstract

Goals of work. Diagnosis and treatment of childhood cancer are continuous stressors in the lives of the entire family involved. Disease-related tools for the assessment of parental stress and adaptation are scarce. For that reason, the Pediatric Inventory for Parents (PIP), a disease-related measure, was translated into Dutch and its psychometric qualities were determined to prove its value. *Methods.* The PIP and three other measures (State-Trait Anxiety Inventory, General Health Questionnaire and Parenting Stress Index, Short Form) were administered to 174 parents of 107 children diagnosed with cancer in three university medical centers in the Netherlands. *Results.* Internal consistency (Crohnbach's α = .94 and .95) and test-retest reliability (Pearson's r between .67 and .87) of the Dutch PIP Total Scales are satisfactory. Validity was illustrated by a high correlation between PIP scores and anxiety and general stress. Confirmatory factor analysis showed acceptable fit to the data for the original four-factor and the one-factor models; the four-factor model showed slightly better fit. *Conclusion.* The PIP can be used in clinical practice to assess disease-related parental stress. Further psychometric testing is highly recommended.

Introduction

When parents are confronted with a cancer diagnosis in their child, they often report to feel as if their world has fallen apart. Although most parents show remarkable resilience over time, for a subgroup of parents, levels of psychological distress remain high throughout the entire treatment period and thereafter [14-16,34,41]. Heightened levels of depression [1,44], anxiety [5,6,30,33], stress [21,30], a decreased quality of life [12], marital distress [10,13] and post-traumatic stress symptoms (e.g. [18,25]) have been reported in parents of pediatric cancer patients. This effect has been found to persist in a substantial proportion of the parents, five to even ten years or longer [21,42]. Distress levels are highest around and shortly after diagnosis [41]. Parents experiencing most emotional problems at diagnosis and during treatment continue to report high levels of distress, even after treatment ends [21,36]. Mothers tend to report more stress than fathers [42,44] and younger parents and parents of younger children report more stress than parents of older children [35].

To obtain a better understanding of parental stress related to pediatric cancer, multidimensional assessment specific to the circumstances of parents of these children is needed [22,36]. In most studies, generic measures of psychological maladjustment have been used to assess parental distress. Significant differences with the reference group were found in some [27], but not in all studies [23]. Some authors argue that these traditional instruments are not sensitive enough to assess emotional and behavioral changes related to medical conditions [3]. However, when no differences are found, one cannot simply conclude that the measures are insufficient; it could also mean that there are in fact no differences between the groups.

Using disease-related measures in combination with generic measures could provide additional information that can be used to study the impact of psychosocial interventions and that will help to guide psychosocial interventions [22]. Several questionnaires have been developed specifically for parents of children with cancer or children undergoing stem cell transplantation [7,11,19,28,32]. The Pediatric Inventory for Parents (PIP) [35] was designed to examine areas of stress and concern in parents of children with a medical illness. It has been proven a reliable instrument for examining parent's report of stress related to caring for a child with a serious illness, such as cancer [35,36], diabetes [37] and sickle cell disease [24]. One of the assets of the PIP is that parents are asked to rate both the frequency of stressful illness-related events and the difficulty they experience with these events. PIP total scores correlated significantly with a generic measure of state anxiety and parenting stress within a childhood oncology population [35].

The availability of assessment instruments in more than one language is low. This is unfortunate, because it would facilitate international multi-center studies and allow for cross-cultural comparisons. However, the translation in another language and culture is a lengthy and laborious process and is not always carried out adequately and/or documented properly in research articles.

The present study evaluates the psychometric qualities of the Dutch PIP, specifically item distribution, test-retest reliability, construct validity (by calculating correlations between the PIP and three other measures) and discriminative validity (i.e. the ability of the PIP to distinguish between known groups). Using confirmatory factor analyses, we evaluated the original four-factor model of the PIP by examining the goodness-of-fit to the data. As the total scales are regularly used and previous studies [31] found substantial correlations (ranging from 0.45 – 0.83) between the four subscales, we also evaluated the comparative fit of the four-factor model versus the one-factor model.

Method

Participants

All parents of children -aged 0 through 18 years- diagnosed with a malignancy 1-18 months ago between January 2005 - February 2007 in three medical centers (Leiden University Medical Centre, Wilhelmina Children's Hospital Utrecht and University Medical Centre Groningen) were asked by letter to participate in the study. We chose to include parents of children diagnosed between 1 and 18 months ago in order to obtain a sample that would be more or less homogeneous with regards to 'time since diagnosis'. Parents of deceased children were excluded from the study. In total 268 parents were approached (78 in Leiden, 60 in Utrecht and 130 in Groningen).

Procedure

The study was approved by the Medical Ethics Committee of all three medical centers. The PIP was translated by a team of five persons. An English 'native speaker' was asked to make a back-translation, according to the procedure described by Van Widenfelt et al. [39]. The author of the PIP provided feedback on the back-translated questionnaire. The translated version was piloted with three couples and adaptations were made if necessary.

Eligible parents received information about the study and an informed consent form. In Leiden, part of the parents (40%) received the questionnaires by mail and part (60%) filled in the questionnaires in the clinic. No differences between the methods were found. Parents were instructed to fill in the questionnaires separately and not to consult each other. In Utrecht and Groningen, questionnaires were mailed to the parents' homes along with the study information and consent forms.

One week after filling in the PIP and other questionnaires, a random half of the parents (every even numbered returned booklet) received the PIP again, to obtain test-retest reliability data. Parents who did not want to participate in the study were asked to supply demographic and illness-related data.

Measures

Parental disease-related stress was measured using the *Pediatric Inventory for Parents (PIP).* The PIP is a 42-item self-report questionnaire that measures parental stress related to the serious illness of the child with respect to (a) communication with the child and the medical team (9 items), (b) emotional distress (15 items), (c) medical care (8 items) and (d) role function (10 items). Each of the 42 items is rated on two 5-point Likert-type scales. Parents need to respond to the items twice: the first time to assess the frequency of each stressor; the second time to assess how difficult the issue has been for the parent. Parents are asked to consider last week when responding to each item. Examples of PIP-items: 'Learning upsetting news' or 'Speaking with the doctor'. Higher scores refer to more stress. Adequate internal consistency (α =.80-.96) and construct validity of the original version of the PIP (scale scores range 42-210) have been reported [35].

Parental anxiety was measured using the *State Trait Anxiety Index, state and trait version (STAI)*, a 40-item questionnaire that measures the respondent's transitory emotional condition of stress and the general inclination towards anxiety. Dutch reference data and information on reliability (Crohnbach's α. 95 and .94) and validity are available [2]. In our study, the alphas were .95 (state anxiety) and .94 (trait anxiety).

Parental psychological distress was assessed using the *General Health Questionnaire (GHQ)*, a 12-item version self-report measure of non psychotic psychiatric disorders that can be used as a general measure for psychological distress. The psychometric properties of the Dutch version of the scale are reported to be good [20] and the questionnaire has been used frequently in research and patient care [40,43]. In our study, the alpha was .87.

Parental stress associated with raising children (i.e. parenting stress) was assessed using the *Parental Stress Index, short form (PSI-SF), Dutch version* [8]. The PSI-SF is derived from the full 123-item PSI. The PSI-SF is a reliable and valid measure and contains 25 items that are scored on a five-point continuum from strongly agree to strongly disagree. The PSI-SF differentiates well between clinical and non-clinical groups and has been used in various studies [38]. In our study, the alpha was .93.

Demographic and clinical information: Gender, age, marital status, educational level of the parent, gender and age of the target child, the child's medical diagnosis, current treatment status and the number of weeks since diagnosis were recorded.

Statistical analyses

To assess differences between responders and non-responders, we used independent T-tests and chi square tests for categorical variables. We evaluated the normal distribution of the PIP with the test of normality and we calculated skewness and kurtosis. Confirmatory factor analysis (CFA) with weighted least squares means and variance adjusted estimation (WLSMV), applied to the polychoric correlation matrix, was used to evaluate the fit to the data of the original and the modified four- and one-factor models. WLSMV has been shown to perform well with ordinal variables and rather small samples [4]. The Mplus program version 2.02 [29] was used for factor analyses.

The fit of the models was assessed using practical fit indices, the values of which were evaluated according to the guidelines formulated by Marsh, Hau, and Wen [26]. The indices included the normed comparative fit index (CFI), the Tucker-Lewis index (TLI), the root mean square error of approximation (RMSEA) and the standardized root mean square residual (SRMR). RMSEA and SRMR values >0.10 are regarded as indication of bad fit, as were CFI and TLI values < 0.85. We used the Cheung and Rensvold [9] CFI-criteria to test the difference between models: changes in CFI (ΔCFI) of –.01 or less indicate that the hypothesis of equal fit should not be rejected, when ΔCFI lie between –.01 and –.02, differences may exist and definite differences between models exist when ΔCFI is greater than –.02.

To compute test-retest reliability we used Pearson's r. To assess internal consistency of the PIP total and the four domain scales Cronbach's coefficient α was calculated. Alpha values of .7 and above were considered adequate. Construct validity was examined by conducting correlation analyses between the PIP and the other psychological measures. The intercorrelations of the PIP subscales were calculated by use of Pearson correlations. To test the discriminative validity, independent T-tests were used to examine the effect of demographic and illness-related variables on stress reported on the PIP.

Results

Participants

The overall response rate was 66% (72 % in Leiden, 65 % in Utrecht and 61 % in Groningen). Six parents were excluded because of missing data. In total, 174 parents of 107 children participated. Of 15 single-parent families and 25 families, only one parent participated.

Reasons for refusal were the experience of too many stressful events (26%), lack of time (18%), the illness and treatment of the child was considered to have been completed too long ago (16%), too busy with work (15%), language problems (13%) or it was too confronting to the parents (10%). Non-participating parents did not differ from participating parents with regard to age, marital status, educational level, sex and age of the child. However, we did find significant differences with respect to parent gender, parent ethnicity and treatment status. In the non-participating group, the percentage of fathers, non-Dutch parents and parents with a child off treatment was higher. See Table 1.

Results on the outcome measures and demographic characteristics did not significantly differ between the three medical centers, hence we analyzed all data together.

Item Distribution and interscale correlation

First, the test of normality was performed on the different subscales and total scales of the PIP. Both total scales showed normality, the subscales significantly deviated from normality, except for two scales. Kurtosis was found for Communication Frequency (3.25, $p < 0.001$) and Emotional distress Frequency (2.76, $p < 0.01$). Skewness was found for the scales Communication Frequency, Emotional distress Difficulty and Role function Frequency. Interscale correlations of the PIP-subscales varied from .50 (Medical care Difficulty with Communication Frequency) to .82 (Communication Frequency with Emotional distress Difficulty).

Reliability

Cronbach's alphas for the Total scales (PIP-Frequency = .94, PIP-Difficulty = .95) and for the subscales Medical Care, Emotional Distress and Role Function (≥ .80) were adequate. The alpha-value for the Communication scale was low for the PIP-Frequency and PIP-Difficulty scales (see table 2a). After deletion of item number 2 *Arguing with family member(s),* the alpha was acceptable (.65).

When analyzing mothers and fathers separately, we found similar reliability scores (see table 2b). Mean scores between mothers and fathers differed significantly (mothers scoring higher, $p < .05$) on the Frequency scales Communication, Medical care and Emotional distress and the Total Frequency score. The Difficulty scale Emotional distress and Total Difficulty scores were also significantly higher for mothers than for fathers.

Test-retest reliability after 14 days was adequate ($.68 \leq r \geq .87$), based on returned questionnaires from 78 parents (33 fathers, 45 mothers) of the 111 parents approached to fill in the PIP twice (70% response rate).

Table 1. Demographic characteristics of parents and children

	Responders	*(N=107)nge*	*SD*	**Non-responders**	*(N=39)*	*SD*
	No. of children:	*(N=174)*		*No. of children:*	*(N=94)*	
Parent characteristics	*M*	**Range**	**SD**	*M*	**Range**	**SD**
Age	41.0	22-65	7.0	40.0	28-60	6.8
	N	*%*		*N*	*%*	
Sex						
Male	74	42.5		52	55.3*	
Female	100	57.5		42	44.7	
Educational level						
Lower	41	23.6		33	35.1	
middle	76	43.7		30	31.9	
higher	57	32.8		31	33.0	
Ethnicity						
Dutch	161	92.5		73	77.7*	
Non-Dutch	13	7.5		21	22.3	
Marital status						
Married/living with partner	161	92.5		87	92.6	
Divorced/widowed/single	13	7.5		7	7.4	
Hospital						
Leiden	56	32.2		22	23.4	
Utrecht	39	22.4		21	22.3	
Groningen	79	45.4		51	54.3	
Child characteristics	*M*	**Range**	**SD**	*M*	**Range**	**SD**
		(N=174)			*(N=94)*	
Age at assessment (months)	115.0	8-218	61.8	106.2	17-230	59.3
Time since diagnosis (weeks)	40.5	5-110	25.3	42.4	8-110	22.0
	N	*%*		*N*	*%*	
Sex						
Male	57	53.3		20	51.3	
Female	50	46.7		19	48.7	
Diagnosis						
ALL/ /JMML	41	38.3		12	30.8	
AML	8	7.5		2	5.1	
(Non)Hodgkin's lymphoma	19	17.7		6	15.4	
Bone tumors[a]	14	13.1		3	7.7	
Brain tumor	11	10.3		4	10.3	
Neuroblastoma	5	4.7		1	2.6	
Wilm's tumor	4	3.7		3	7.7	
Other	5	4.7		8	20.5	
Treatment status						
On treatment	86	80.4		17	43.6*	
Off treatment	21	19.6		22	56.4	

[a] Ewing sarcoma, osteosarcoma and synovia sarcoma

ALL = acute lymphatic leukaemia, JMML = juvenile myelomonocytic leukaemia, AML = acute myeloid leukaemia

* Significant difference between responders and non-responders ($p < 0.05$)

Table 2a. Means, Standard Deviations, and Internal Consistency of the Pediatric Inventory for Parents ($N = 174$)

	PIP-F			PIP-D		
	M	(SD)	α	M	(SD)	α
I. Communication	23.2	(4.5)	.60	18.6	(5.4)	.73
II. Medical care	24.0	(7.2)	.85	16.9	(6.2)	.84
III. Em. distress	43.1	(10.1)	.88	44.6	(12.6)	.91
IV. Role function	25.1	(7.1)	.80	21.6	(7.4)	.82
Total	115.4	(26.0)	.94	101.7	(28.5)	.95

PIP F = PIP Frequency, PIP D = PIP Difficulty, Em. = emotional

Table 2b. Means, Standard Deviations, and Internal Consistency of the Pediatric Inventory for Parents, mothers ($N = 100$) and fathers (N=74)

	PIP-F mothers			**PIP-D mothers**			**PIP-F fathers**			**PIP-D fathers**		
	M	**(SD)**	α	**M**	**(SD)**	α	**M**	**(SD)**	α	**M**	**(SD)**	α
I. Communication	24.3*	(4.9)	.52	19.1	(5.1)	.73	22.0	(4.6)	.69	17.9	(5.7)	.82
II. Medical care	25.3*	(7.1)	.83	17.5	(5.9)	.81	22.2	(6.9)	.84	16.2	(6.6)	.83
III. Em. distress	44.2*	(11.3)	.75	46.7*	(12.1)	.90	40.8	(9.5)	.82	41.7	(12.7)	.85
IV. Role function	25.8	(6.9)	.76	22.1	(7.1)	.78	24.1	(7.3)	.88	20.9	(7.7)	.92
Total	120.6*	(26.3)	.95	105.4*	(27.4)	.94	109.3	(25.7)	.95	96.8	(29.3)	.99

PIP F = PIP Frequency, PIP D = PIP Difficulty, Em. = emotional

* Significant difference between mothers and fathers ($p < .05$)

Confirmatory Factor Analyses

Two identical factor models for the PIP-frequency and the PIP-difficulty items were (comparatively) evaluated: a four- and a one-factor model. The one-factor model, constituted by all 42 items of the PIP, reflects the possibility that one single latent dimension underlies the items. The factors of the four-factor model represent the original four scales; the factors were allowed to correlate. The fit index values are presented in Table III. Results indicated adequate fit of all models on the TLI but a bad fit on the remaining indices for all models except the four-factor model for the Difficulty items.

We evaluated areas of strain in the factor models using the modification indices of ML estimation. Error-correlations > 0.100 between item pairs, indicating not modeled minor factors, were found for 5 item pairs in all models: between item pairs 14-16 (indicating a minor factor 'distress over child suffering'), and between the item-pairs 24-29, 24-39, 26-29, 29-36 (indicating a minor factor 'worrying about the child's future'). After adding the 5 error-correlations to the models, good fit on TLI and (nearly) acceptable fit on the remaining indices was found for all models (see Table 3).

The differences in fit to the data between the adjusted four- and one-factor models were negligible, as indicated by ΔCFI< 0.10. Therefore, the one-factor models, representing the Total scales, may be preferred.

Table 3. Goodness of Fit Indices for PIP Four-Factor and One-Factor Models*

Models	χ^2	*df*	CFI	TLI	RMSEA	SRMR
Frequency						
Four-Factor Model	270.04	88	0.869	0.933	0.109	0.091
One-Factor Model	292.91	88	0.852	0.924	0.105	0.091
Four-Factor Model with $\theta_{14,16}$ $\theta_{24,29}$,$\theta_{24,36}$, $\theta_{26,29}$, $\theta_{29,36}$ free	239.35	88	0.891	0.944	0.099	0.084
One-Factor Model with $\theta_{14,16}$ $\theta_{24,29}$ $\theta_{24,36}$, $\theta_{26,29}$, $\theta_{29,36}$ free	249.95	88	0.883	0.940	0.103	0.086
Difficulty						
Four-Factor Model	235.73	88	0.895	0.956	0.098	0.081
One-Factor Model	253.06	87	0.882	0.950	0.105	0.085
Four-Factor Model with $\theta_{14,16}$ $\theta_{24,29}$,$\theta_{24,36}$, $\theta_{26,29}$, $\theta_{29,36}$ free	204.44	87	0.909	0.962	0.091	0.079
One-Factor Model with $\theta_{14,16}$ $\theta_{24,29}$ $\theta_{24,36}$, $\theta_{26,29}$, $\theta_{29,36}$ free	227.85	87	0.900	0.957	0.096	0.082

*: weighted least squares means and variance adjusted estimation was applied to the polychoric correlation matrix; CFI = Comparative Fit Index, TLI = Tucker-Lewis index, RMSEA = Root Mean Square Error of Approximation, SRMR = Standardized Root Mean Square Residual.

Construct Validity

Correlations between the PIP total scales and the other instruments were calculated. For all parents, the PIP-Frequency scale was strongly associated with STAI state and trait (r = .52 and r = .55, p < .01) and with the GHQ (r = .54, p < .01) and weakly with the PSI-SF (r = .19, p < .05). The PIP-Difficulty scale was strongly related to STAI state and trait and GHQ (r = .59, r = .66 and r =.51 respectively, all p < .01) and weakly with the PSI-SF (r = .24, p < .01). When analyzing fathers and mothers separately, the correlations were comparable.

Discriminative validity

Mothers reported higher scores than fathers (PIP-Frequency, p < .01, t = 2.84). Older fathers (i.e. fathers above the mean age of 41 years at assessment) reported significantly more distress than younger fathers (PIP-Difficulty, p < .05, t = 2.19). Interestingly, older fathers also reported significantly higher state anxiety levels. For mothers, no age effect was found. Parents of younger children (under versus over 115 months) reported higher stress scores than parents of older children (PIP-Difficulty, p < .05, t = 2.11).

Parents of children on treatment had significantly higher PIP scores than parents whose children had completed treatment (PIP-Frequency, p < .05, t = 2.92) and parents of children diagnosed more recently –less than 40 weeks ago- reported more stress (PIP-Frequency, p < .05, t = 2.49) than parents of children who were diagnosed longer ago.

Item-subscale and item-total correlations

Item-subscale correlations varied from -.07 to .67 in the Frequency Scale, with a mean of .46. For the Difficulty items, item-subscale correlations varied from .23 to .79 with a mean of .53. Lowest item-subscale correlations were found for the scale Communication. Item-total correlations varied from .02 to .70 for the Frequency items (mean .47) and from .32 to .77 for the Difficulty items (mean .55).

Discussion

Gaining insight into parents' stress following pediatric cancer is increasingly important in order to deliver adequate psychosocial care to the entire family. Disease-related measures can add important information about parental adaptation to stressful illness-related situations. Results regarding the Dutch version of the Pediatric Inventory for Parents (PIP), a disease-related measure of parental stress, are satisfactory. We found adequate (test-retest) reliability scores for the PIP Total scales and three of the four subscales (Medical care, Emotional distress and Role function). The fourth subscale, Communication, needs improvement. This last finding is not in line with the results from the original study [35]. Cultural differences with regards to communicating with hospital staff and family could perhaps explain part of this difference in results.

PIP scores correlated strongly with a generic measure of anxiety and general psychological functioning. This means that disease-related distress, although it measures a different construct, can have considerable overlap with general well-being and anxiety. The added value of the PIP however is that it asks parents about their stress concerning disease-related situations. Scores on the PIP could be transformed into an individual 'stress profile', which could be used to tailor psychosocial support.

The low correlation of PIP scores with parenting stress scores suggests that stress resulting from difficulties disciplining and setting limits to one's child (parenting stress) differs from stress associated with having a child with a serious illness (parental stress). In various studies, e.g. [17], the PSI is used as a measure of parental stress instead of stress associated with parenting. This strategy might well result in drawing the wrong conclusions about the stress reactions parents can have as a result of their child's illness.

As expected and in line with other research [33,44], mothers showed higher PIP-scores than fathers, parents closer to diagnosis and parents of younger children reported more stress. Older fathers reported higher stress levels. For mothers, no age effect was found. This result is contrary to the findings of the original PIP-study, in which younger parents (both mothers and fathers) reported more stress [35].

Confirmatory factor analyses showed that not only the four factor model, representing the four subscales of the PIP, but also the one-factor model, representing the Total scales, showed acceptable fit to the data after three items were dropped from the models and the error-correlation of one item-pair was added. The Total scales may be regarded as sufficient for practical purposes as the difference in fit between the two models were minor, and very strong correlations were found between the four latent factors.

On of the advantages of the PIP is subdivision of parental stress levels into Frequency and Difficulty scores (even though the scales correlate highly and thus outcomes might be partly overlapping), which enables the psychosocial team to target interventions more precisely to the needs of parents in different phases of their child's treatment. In our study, PIP-Frequency scores discriminated between parents of children on treatment and parents whose children have ended treatment. However, PIP-Difficulty scores for the two groups were equal. This finding may imply that although the frequency of stressful disease-related events is lower in parents of children off treatment, the perceived difficulty of these events remains similar.

Limitations and practical implications

Despite the results of the present study, there are some limitations that need mentioning. Firstly, the age range of the children in our study group varied widely, making comparison of parental stress levels difficult. Being the parent of an ill baby or toddler versus a teenager will render different sources of stress. Secondly, a substantial proportion of parents refused participation. Reasons for non-participation ranged from being too stressed to considering the treatment of the child to have been completed too long ago or being too busy with other things like work. It is unclear if this caused an under- or overestimation of parental stress levels.

Lastly, the procedure of administering the questionnaires was different in the three hospitals. Approaching parents face to face in the clinic or the outpatient's ward yielded a higher response rate than mailing the questionnaires. However, this did not seem to influence reported levels of stress.

One of the assets of the study is the relatively large, multi center study group. Furthermore, we managed to include a large percentage of fathers in our study. The PIP could be used in regular patient care to assess all parents of newly diagnosed children at critical time points in therapy: shortly after diagnosis, then again after 4-6 months (usually seen as the 'stabilization phase') and by the end of treatment. These time points seem to cover the process of parental stress through the phases of childhood cancer well.

In summary, the Dutch PIP is a reliable and valid assessment tool to gain insight in stress experienced by parents during the course of their child's cancer treatment. Continuous psychometric testing is recommended in different populations and at different time points.

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Parental stress before, during, and after pediatric stem cell transplantation: a review article

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Abstract

Goals of work. Pediatric stem cell transplantation (SCT) is a stressful treatment for children with relapsed or high-risk malignancies, immune deficiencies and certain blood diseases. Parents of children undergoing SCT can experience ongoing stress related to the SCT period. The aim of this article was to present a literature review of articles on parental distress and adaptation before, during, and after SCT and to identify risk and protective factors. *Methods.* The review was conducted systematically by using PubMed, Web of Science, PsychInfo and Picarta databases. Eighteen articles met our inclusion criteria: publishing date between January 1, 1990 and January 1, 2009; studies concerning parents of children undergoing SCT; studies examining the psychological adjustment and/or stress reactions of parents as primary outcomes and studies available in English.
Results. Highest levels of parental stress are reported in the period preceding SCT and during the acute phase. Stress levels decrease steadily after discharge in most parents. However, in a subgroup of parents, stress levels still remain elevated post-SCT. Parents most at risk in the longer term display highest levels of stress during the acute phase of the SCT. *Conclusion.* Psychosocial assessment before SCT, during the acute phase and in the longer term, is necessary to identify parents in need for support and follow-up care.

Introduction

Stem cell transplantation (SCT) is an invasive treatment for seriously ill children who have hematological, oncological, or metabolical diseases. Recently, for some high-risk leukemia protocols, SCT has become close to being a first-choice treatment. SCT is a perilous treatment, associated with significant mortality and morbidity [5]. It involves a lengthy hospital admission in an isolated environment to prevent infections and treatment with high doses of chemotherapy and/or radiation, followed by infusions of donor stem cells [22]. During the acute phase of SCT, children report high levels of somatic distress, mood disturbance [30], nausea and pain [7], and fatigue and malaise [29]. In the first 4-6 months post-SCT, children are still susceptible to infections and need to live with restrictions. SCT has a profound impact on the lives of children and parents, both during the acute phase and afterwards. Parents are faced with the need to provide both physical and emotional care for their ill child during a long and stressful period. Furthermore, they have to deal with their own emotions, especially with the realistic fear of losing their child and they have to make complicated decisions about the treatment together with the multidisciplinary team. Some parents are also faced with supporting one of their other children who will be acting as a sibling donor and increasingly, parents are acting as haploidentical donors themselves in the case no appropriate donor has been found.

Despite improved survival rates, SCT remains a high risk procedure. The result of the transplantation depends on several risk factors, including type and status of the underlying disease [5]. After treatment, parents and children are faced with the risk of recurrence, acute or chronic graft-versus-host disease (GVHD), and numerous possible late effects such as pulmonary disease, growth problems, and infertility [4,21]. Even in the longer term, the child's illness and the SCT may influence parents' everyday lives [8]. SCT treatment protocols have changed in the past decades, one of the most important differences between treatment now and in the 1990s is the shortened admission period. On the one hand this is an improvement because parents may have fewer concerns about the practical issues during admission, e.g. being away from home for a long period and dealing with work-related stress. On the other hand, caring for a child at home post-SCT can be a heavy burden on parents and families. In addition, increasing survival rates entail increasing numbers of survivors with possible long-term side effects. Moreover, the fear of losing the child is still realistic. Accordingly, changed treatment protocols may not make any difference for parental stress levels.

The field of parental adaptation to their child's SCT has gained more attention in the past decade; most studies have been conducted in the past 8 years [18,31]. The majority of studies have focused on parental stress and adjustment pre-SCT, during the acute phase, and 3, 6, or 18 months post-SCT, e.g. [5,18]. These time points seem to cover

the SCT time frame well: 3 months post-SCT, many children still suffer from the after effects of the SCT, whereas after 6 months, most of the children can return to school and pick up their old lives, even if their health is suboptimal [1]. Twelve to eighteen months post-SCT, the majority of children report to have a health-related quality of life (HRQoL) comparable to healthy peers [2,7]. However, certain aspects of HRQoL seem to be affected in the long-term in many survivors, for example cognitive functions and pain, which has been demonstrated recently by Löf et al. [15].

No review articles have been published in this specific area so far. In related areas, however, review studies have focused on adjustment and coping of parents of children with cancer [9,40]; on the quality of life and/or emotional adjustment of children after SCT [2,38]; on the psychological adjustment of families of adult SCT patients [14] and on the psychosocial impact of SCT of adult patients [11,23]. The aim of our article was to conduct a systematic review of the current literature (1990 to 2008) on parental distress and adaptation to their child's SCT and to identify risk and protective factors.

Methods

Search strategy for identification of studies

Several research engines were used to obtain the studies included in this review: Pubmed, Web of Science, PsychInfo, and Picarta. These databases were searched for one of the words: BMT, bone marrow transplantation, SCT, or stem cell transplantation combined with the following words used in headings, keywords, subjects, or abstracts: pediatric, paediatric, parent, child, mother, father, AND/OR stress, distress, post-traumatic stress disorder (PTSD), Post-traumatic stress symptoms (PTSS), anxiety, depression, parental stress, parental distress, psychological, adjustment, and coping. Subsequently, reference lists of the relevant articles were examined to identify additional papers that met the search criteria and a hand search was conducted in several relevant academic journals.

Criteria for considering studies for the review

Criteria for inclusion were: publishing date between January 1, 1990 and January 1, 2009; studies concerning parents of children undergoing SCT; studies examining the psychological adjustment and/or stress reactions of parents as a primary outcome; and studies available in English. Exclusion criteria were: reviews, guidelines, protocols, commentaries, and other descriptive articles; studies focusing on psychological adjustment of pediatric SCT patients only; studies focusing on other critical illnesses or including other treatments; and studies focusing solely on intervention programs.

Description of the studies

Eighteen studies were selected for this review. Table 1 contains a descriptive summary of the articles. We included the aim of the study, number and characteristics of parents and children, methodological features (e.g. study design, timing of measurement); measures; and main results. The indications for SCT varied among the different studies. Most studies reported the underlying diagnosis, type of transplant and type of donor, transplant risk, and disease risk category [17]. On average 80% of the children undergoing SCT suffered from a malignant disease and around 60% of the children in the studies underwent allogeneic SCT (transplantation with bone marrow from a foreign donor) as opposed to autologous SCT (transplantation with own body material). The studies in our review did not distinguish between the experiences of parents of children undergoing SCT once and parents of children who had multiple SCT experiences, who will undoubtedly have to face a unique set of stressors.

In this review article, we will first discuss the methodological qualities of the studies, next we will summarize the main results of the studies, and lastly we will discuss risk and protective factors of parental adaptation to their child's SCT.

Methodological qualities of the selected studies

Study design and timing of assessment

Three of the included studies used a cross-sectional study design [3,20,27] and one study was descriptive/retrospective [8]. The other 14 studies used a prospective longitudinal design with repeated measures, ranging from two to 13 measurement points. However, only a few of these studies followed a particular aspect of parental distress over time, e.g. [18,32]. Exactly half of the studies included in the review used a multi-centered design, the other nine studies recruited participants from one medical center. Until now, only one intervention study has been published in this area. It included mothers of children undergoing SCT [36] and was based on a stress inoculation model.

In most longitudinal studies, two measurement points were used. The first time point was between 47 to 1 day(s) pre-admission and a few days post-SCT. The time point for the second assessment varied strongly between the studies, ranging from 1 week post-SCT to18 months post-SCT. Phipps et al. [31,32] used up to 13 time points in both studies. Only one of the studies assessed long-term parental distress, 4 to 8 years after stem cell transplantation [8].

Participants

The majority of the studies (13 in total) used only mothers as respondents. Sample size in the studies varied from 11 [36] to 207 parents [18]. Eleven of the studies included more than 90 parents. All studies described the recruitment process. Phipps et al. [31,32]

assessed one of the caregivers, resulting in 90% mothers. In only three studies [3,27,39], both parents were used as respondents. The age range of the children was most often 1 to 20 years of age with a mean age at first assessment between 8 and 9 years. In two studies, the age of the children was not mentioned [8,27].

Outcome measures

The conceptualization of stress or distress varied widely between the studies. The distinction between the assessment of (subclinical) levels of distress on the one hand and clinical psychiatric diagnoses was not always clearly made, which makes comparisons difficult. Anxiety and depression were studied as manifestations of parental distress in nearly all of the studies. Other manifestations of parental distress or psychiatric disorders were disturbed and obsessive-compulsive thinking [3], post-traumatic stress symptoms [16,17], generalized anxiety disorder (GAD), panic disorder (PD), and major depressive disorder (MDD) [20]. Somatic complaints and changes in sleep behavior were added by some researchers [25,34,35] as symptoms of parental distress. Variables influencing parental stress levels were mostly operationalized as 'coping' [18,24,25,32], 'family functioning' [32], 'parenting stress issues' [39] and 'social support', both positively and negatively perceived [19,25,32].

In most studies multiple measures were used, most often self-report questionnaires combined with, or additional to, interviews as a way of collecting data. In the majority of studies standardized questionnaires were used to assess parental distress reactions (e.g. Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), State-Trait Anxiety Inventory (STAI), and Parental Stress Index (PSI)), e.g. [17,20]. Disease- or context-specific measures were used less frequently. Phipps et al. [31,32] developed and used the Prior Illness Experiences Scale (PIES) to assess previous parent and child experiences with cancer therapy and inpatient hospitalization. Rini et al. [35] created two items to measure benefit finding in their study and DuHamel and her study group developed a scale to assess maternal fear appraisals [6].

Table 1. Summary of the studies included in the review

No	*Year, Author*	*Aim*	*N parents N and age range/ mean age children*	*Methodological features*	*Measures*	*Results*
1	1990, Dermatis	Determine the nature and prevalence of the psychological symptomatology in parents of children undergoing SCT. Investigate relationship of certain psychosocial factors to parental distress associated with the informed consent process.	46 M, 15 F 61 children Range 1-17 yrs	Single-centered Cross-sectional	BSI, WOC, newly constructed scale on the quality of the physician-parent communication	47% of fathers and 60% of mothers exhibited significant psychological distress of a generalized nature. Mothers reported more severe levels of depression and anxiety than fathers did.
2	1997, Nelson	Examine the stress responses of mothers during their child's hospitalization for SCT; Determine the relationships between mothers' stress responses and the resources for coping and social support.	50 M 50 children Mean age 9.3 yrs	Single-centered Longitudinal, time points: time of admission (T1), second (T2), tenth (T3) and twentieth (T4) day post-SCT	STAI, CES-D, HAS, IES, SSS	Maternal anxiety and depressive scores decreased significantly over time The coping style defined as 'active reviewing of feelings or information associated with the situation' significantly explained variance in scores for anxiety, depressive symptomatology, somatic complaints and sleep behavior.
3	2000, Streisand	Document levels of stress in mothers of children undergoing SCT. Pilot a psychological intervention program.	11 M 11 children Range 2-16 yrs Mean age 8.8 yrs	Single-centered Longitudinal, time points: pre admission to 3 weeks post-SCT	DSI, PSI, SSINT	Most stress was reported pre-admission. Mothers reported using more stress management techniques post-intervention than mothers in the standard care condition. The analyses revealed no significant differences in stress between intervention and control mothers.
4	2001, Manne	Examine anxiety and depressive symptoms among mothers of children undergoing SCT.	115 M 115 children Range 4 months-20 yrs Mean age 9.2 yrs	Multi-centered Cross-sectional: 85% of mothers on day -7 to day -1; 15% of the mothers 10 days post-SCT	BAI, BDI, SCID-NP	20% of mothers were diagnosed with a MDD, a GAD, or a PD. There was evidence of comorbidity between anxiety and depressive disorders. Mothers with lower incomes, who were Caucasian, had received prior psychiatric care and were caring for female SCT patients may be at higher risk for adverse psychological reactions.
5	2002, Manne	Investigate the role of cognitive and social processing in post-traumatic stress symptoms and disorder (PTSD) among mothers of children undergoing SCT.	90 M 90 children Range 9 months-20 yrs Mean age 8.8 yrs	Multi-centered Longitudinal, time points: time of SCT, 3 and 6 months past SCT	SCID-NP-PTSD, PCL-C, BAI, BDI, fear network, CSI, LSCM	Emotional distress, SCT-related fears, and negative responses of family and friends assessed at the time of SCT hospitalization were predictive of later PTSD symptoms. Cognitive processing (the appraisal of threat) at the time of transplantation played the most important role in later PTSD symptoms.
6	2002, Oppenheim	Understand parents' perception of children treated in an SCT unit.	40 pairs of parents No details given	Single-centered Cross-sectional	Interviews	Parents expressed intense distress and disorientation and sometimes difficult relations with their child. Many parents expressed having an ambivalent relation with care providers.

No	*Year, Author*	*Aim*	*N parents N and age range/ mean age children*	*Methodological features*	*Measures*	*Results*
7	2003a, Manne	Evaluate the role of maternal coping strategies in depressive symptoms experienced by mothers of children undergoing SCT.	207 M 207 children Mean age 8.3 yrs	Multi-centered Longitudinal, time points: at SCT, 3 and 6 months post-SCT	COPE, BDI, appraisal of fear/ worry medical risk	Acceptance and humor were associated with reductions in maternal depressive symptoms. Planning and alcohol/ substance use were associated with increases in maternal depressive symptoms. Active problem solving and use of instrumental support did not predict changes in depressive symptoms.
8	2003b, Manne	Examine the role of perceived partner criticism and avoidance in anxiety and depressive symptoms of mothers of children undergoing SCT.	148 M 148 children Range 4 months-17 yrs Mean age 8.5 yrs	Multi-centered Longitudinal, time points: at SCT, 3 and 6 months post-SCT	SCID-NP-PTSD, PCL-C, BAI, BDI, Fear Network, CSI, CSI, LSCM	Fear structure, distress, and unsupportive responses by family and friends measured at transplantation were predictive of PTSD symptom severity at 6 months after SCT. Perceived partner criticism was associated with higher average depressive symptoms. ICU transfers and number. of days of hospitalization 6 months post-SCT were risk factors.
9	2003, Nelson	Examine the relationships between maternal anxiety and depressive symptoms and resources during their child's SCT.	23 M 23 children Mean age 8.1 yrs	Single-centered Longitudinal, time points: admission and 10 days post-SCT	STAI, CES-D, SPSI, SSS	The majority of mothers reported moderate to high anxiety levels and were at risk of developing depression. Most of the mothers indicated low or moderate satisfaction with the perceived social support. A relationship was found between a negative problem solving orientation and emotional responses.
10	2004, DuHamel	Investigate the role of cognitive processing in maternal adjustment to a life-threatening pediatric medial procedure.	91 M 91 children Range 9-19 yrs Mean age 8.7 yrs	Multi-centered Longitudinal, time points: 3 days prior to SCT and 3 months post-SCT	Structured interviews Fear network IES, BAI, BDI	Mothers' fear network, intrusions and avoidance played a primary role in their adjustment to their child's transplantation, during and after hospitalization. The article shows a cognitive processing model of psychological distress.
11	2004, Forinder	To get in-depth knowledge of the parents' situation during the SCT-process.	20 pairs of parents 20 children, no details given	Single-centered Longitudinal, time points: 4 to 8 yrs post transplant and 4 yrs after first time point	2 semi-structured qualitative interviews Jalowiec Coping Scale	The child's illness and treatment played an important role in the parents' lives for many years. Those parents who managed to put reason before emotion rated their coping as better. A sense of participation was also a useful coping strategy.
12	2004, Manne	Examine the prevalence and predictors of anxiety, depression and PTSD among mothers of children who underwent HSCT.	111 M 111 children Range 1-18 Mean age 8.2 yrs	Multi-centered Longitudinal, time points: at time of SCT and 18 months post-SCT	BAI, BDI, TSS, ISSB, WOC, COPE 18 month follow up: SCID-NP	Approximately 20% of mothers had clinically significant distress reactions. Mothers who were most at risk were younger and reported anxiety and depressive symptoms at the time of transplantation. The prevalence of depressive disorders declined after 18 months.
13	2004, Phipps	Examine changes in parental distress across the acute phase of SCT. Examine the relationship of parental distress to child distress during the SCT process.	136 M, 9 F, 6 others 136 children Range 1-20 yrs Mean age 8.9 yrs	Single-centered Longitudinal, 13 time points: weekly from week -1 to week +6, after that on a monthly basis through month +6	POMS, PSS, CBS, BASES-P, BASES-C	Parents demonstrated modest, but significant elevations in distress, particularly during the early period from admission through week +3. Parental distress was unrelated to child age, gender, diagnosis, or type of transplant, but was significantly related to parental SES. Moderate correlations were observed between measures of parent and child distress.
14	2004a, Rini	Examine the relation between life stress and basic beliefs about self-worth.	100 M Range 9 months-20 yrs Mean age 8 yrs	Multi-centered Longitudinal, time points: at admission and 1 year post-SCT	WAS, TSS, LES, SF36	Prior trauma and negative events were associated with basic beliefs during hospitalization and with changes in basic beliefs in the subsequent year, with distress mediating some of these relations. Relations were found between basic beliefs and maternal physical and mental functioning.
15	2004b, Rini	Examination of children's medical risk and mother's dispositional optimism and socio-demographic resources as predictors of benefit finding at admission (T1) and 6 months later (T2).	144 M 144 children Range 9 months-20 yrs Mean age 8 yrs	Multi-centered Longitudinal, time points: at admission and 6 months after the first time point	LOF, SF-36 (MHSS), 2 newly created items for benefit finding	Predictors of benefit finding differed systematically across assessments, with optimism and medial risk predicting benefit finding at both time points. Socio demographic resources predicted only T2 benefit finding. T1 benefit finding was positively associated with T2 adaptation only for mothers who scored high in optimism.
16	2005, Phipps	Examine psychosocial predictors of distress in parents of children undergoing SCT.	139 M, 9 F, 3 others 151 children Range 1-20 yrs Mean age 8.9 yrs	Single-centered Longitudinal, time points: weekly basis through week +6 post-SCT, monthly until +6	POMS, PSS, CBS, PIES, CBCL, FES, ISSB, WOC	Significant changes were observed in parental distress across the course of SCT, with relatively high levels of parental distress at admission, slightly increasing and peaking at week +2. Predictors of stress: prior parent and patient illness-related distress, pre-morbid child internalizing behavior problems, the family relationship dimensions of the family environment and parental avoidant coping behaviors.
17	2007, DuHamel	Investigate several potential antecedents of maternal fear appraisals: maternal optimism, recent negative life events, lifetime history of traumatic events, and medical characteristics.	140 M 140 children Range 9 months-19 yrs Mean age 8 yrs	Multi-centered Longitudinal, time points: at admission, 3 and 6 months post-SCT	LOT, LES, TSS, newly created items for fear appraisals	Lower optimism and a greater number of negative life events were independently associated with greater maternal fear appraisals. Lifetime history of trauma was not associated with maternal fear appraisals. Mothers' fear appraisals during their child's hospitalization were associated with their fear appraisals up to 6 months later.
18	2008, Vrijmoet-Wiersma	To assess levels of parenting stress compared to a norm group, to assess differences in parenting stress pre- and post-SCT and to assess the effect of parenting stress on parent-reported HRQoL of the child.	19 M 21 children Range 3-18 yrs Mean age 8 yrs	Single-centered Longitudinal, time points: two weeks before SCT and on average 10 months post-SCT	PSI	Compared to parents of healthy children, parenting stress was higher post-SCT. Post-SCT, parenting stress levels were higher than pre-SCT, both total parenting stress and the perceived demandingness of the child. High levels of parenting stress were predictive of poor parental ratings of child HRQoL post-SCT.

Explanation of abbreviations used

M= mothers; F= fathers; yrs = years
BAI = Beck Anxiety Inventory; BASES-P/C = Behavioral, Affective, and Somatic Experiences Scales – Parent version/Child version; BDI = Beck Depression Inventory; BSI = Brief Symptom Inventory; CBCL = Child Behavior Check List; CBS = Caregiver Burden Scale; CES-D = Center of Epidemiologic Studies Depression Scale; CSI = Cancer Support Inventory; DSI = Daily Stress Inventory; Faces III = Family Adaptability and Cohesion Evaluation Scale; FES = Family Environment Scale; HAS = Health Assessment Scale; IES = Impact of Events Scale; ISSB = Inventory for Socially Supportive Behaviors; LES = Life Experiences Survey; LOF = Life Orientation Test; LSCM = Lepore's Social Constraints Measure; MHSS-SF36 = Mental Health Summary Scale of the Short Form-36; PCL-C = Post-traumatic Symptom Disorder Checklist-Civilian version; PIES = Prior Illness Experience Scale; POQOLS = Pediatric Oncology Quality of Life Scale; POMS = Profile of Mood States; PSI = Parenting Stress Index; PSS = Perceived Stress Scale; SCID-NP = Structured Clinical Interview for DSM-IV, Non-Patient version; SSINT = Semi-structured Interview; SSS= Stress Support Scale; STAI = State-Trait Anxiety Inventory; TSS = Traumatic Stress Schedule; VABS = Vineland Adaptive Behavior Scales; WAS = World Assumptions Scale; WOC = Ways of Coping Checklist.

Results

Parental stress

Feelings of anxiety and depression, post-traumatic stress symptoms, disturbed or obsessive compulsive thinking and somatic complaints are the most common stress reactions parents report before, during and after SCT. Parental stress levels were reported to be higher than norm groups pre-transplant [3,32,36] and during the acute phase of the SCT, peaking at two to three weeks post-SCT [32]. The most common observation was that parental distress levels decreased over time after SCT [5,36], with the sharpest declines between 3-6 months post-transplant [28]. A recent study however showed that parents, on average 10 months post-SCT, reported higher parenting stress levels and, specifically, felt less competent as a parent [39]. In the longer term, 4 to 8 years post-SCT [8], many parents reported that their child's illness and subsequent treatment played an important role in their lives for years, ranging from parents still struggling on a daily basis to parents who put this ordeal more or less behind them. Studies comparing mothers and fathers are few in this area, since most studies included mothers only. Dermatis and Lesko [3] found higher levels of depression and phobic anxiety in mothers than in fathers.

Table 1 depicts the results of the 18 studies included in the review.

Risk and protective factors

Many factors have been identified to influence levels of parental distress. The most frequently identified risk factor for parental distress in the longer term is the manner in which the parent is able to handle stress during the acute phase. We grouped the risk factors into three clusters, based on a manual count of the determinants described in the included studies:

1. Disease factors, i.e. if the child had been transferred to the ICU and if it had had a higher number of hospitalizations 6 months post-SCT, parents reported more anxious and depressive symptoms [19]. Higher transplant risk was also associated with higher parental distress during the child's post hospital stage of recovery [6].

2. Psychological factors and parental coping: mother's appraisal of threat to her child's life [5,16], a greater number of negative life events [6], prior parent and patient experiences of distress associated with the child's illness [32], avoidance and intrusions [18,32], alcohol/substance abuse [18], perceived partner criticism [19], and an unsupportive family environment [32] all added to parental (i.e. mostly maternal) stress levels. Furthermore, mothers experiencing depressive symptoms during the acute SCT phase had a higher probability to be diagnosed with a psychiatric disorder 18 months post-SCT [17]. Parent distress has also been associated with child distress: child mood disturbance at admission was predictive of parent global distress over time [28].

3. Socio-demographic risk factors: younger maternal age [17] and lower social economical status (SES) [31] were associated with higher levels of stress throughout the SCT process.

Factors that did not appear to influence parental stress were: the age of the child, type of diagnosis, type of transplant, or the nature of the germ-free environment in which the child was placed [3,5,32]. Other objective medical aspects of the child's condition (i.e. disease risk, treatment course, and current disease status) than the factors mentioned under the first cluster (see above) were not related to parental stress levels or fear appraisals. It seems that the subjective appraisal of these factors is a better predictor of parental stress than the objective disease characteristics [6].

Protective factors or predictors of good psychological adaptation have been identified in terms of 'benefit finding' [35]: mothers who were optimistic by nature reported most benefit finding both during the acute SCT phase and 6 months later. Benefit finding is defined as 'an attempt to restore positive basic beliefs about the self and the world that have been challenged by a traumatic experience' [35,37]. Acceptance and humor as coping mechanisms were associated with reductions in maternal depressive symptoms [18] and 'putting reason before emotion' was identified as another coping mechanism associated with positive outcomes [8]. Lastly, a supportive family environment was associated with lower distress levels throughout the transplant process [32].

Discussion

Having a child undergo stem cell transplantation is a stressful event for any parent. Feelings of anxiety and depression, post-traumatic stress symptoms, disturbed or obsessive compulsive thinking, and somatic complaints are the most common stress reactions parents report before, during, and after SCT. The process of SCT is comprised of several phases and distress levels seem most elevated in the pre-SCT phase and the acute phase during hospitalization, but can stay elevated after discharge. Most parents return to healthy levels of psychosocial functioning 18 months post-SCT, but a subset of parents reports persistent symptoms years later in terms of anxiety, depressive feelings, and post-traumatic stress symptoms (arousal, avoidance, and recurring memories). Certain maternal coping strategies (e.g. acceptance, humor, putting reason before emotion, and having positive cognitive appraisals) during the acute phase of SCT have been identified as protective factors.

It has been shown that dispositional factors and prior experiences influence the way an individual appraises an event such as SCT and adjusts to it. For example, mothers who were more optimistic by nature reported lower fear appraisals at the time of their child's hospitalization for SCT [6] and later on, post-SCT. Optimism seems to be a more

or less stable trait that can serve as a coping mechanism and a buffer [10], like positive reframing [18] and benefit finding [35]. Mothers who have encountered more negative life events in the months before their child's SCT reported more fear appraisals. It is hypothesized that traumatic events can trigger increased arousal, cognitions that one's life is difficult and traumatic [17], and a tendency to interpret potentially harmful new events more negatively [6]. Pre-existing factors should be assessed and used as starting points for psychosocial interventions.

The present review reveals potential areas of improvement in future research. In the 18 studies included in this review a variety of definitions of the core elements of the psychological stress process have been used, often described together and simply referred to as 'stress'. It is important to clarify what is meant by 'stress' and to specify both the temporal course of a stressor [13] and to identify SCT-specific stressors. Post-traumatic stress reactions imply an existential challenge, but findings suggest that the complex situation of SCT involves several different stressors for the parents. To facilitate communication and collaboration it is necessary to be more specific in the terminology used to describe the psychological reactions of both parents and patients and to make a clear distinction between stress as a predictor variable and psychological stress as an outcome.

In most of the research in this area, no distinction was made between subclinical manifestations of parental distress versus psychiatric states. This is unfortunate, because in the latter approach, parents tend to be 'pathologized' [33] instead of assuming that the majority of families with a seriously ill child are competent and adaptively organized families, without any elevations in their a priori risk (as a group) for psychopathology [12]. Furthermore, it seems that in multidisciplinary SCT teams often there is no consensus of what is 'normal' distress or 'adequate coping' in this context. For example, young and inexperienced nurses can get worried about a parent in tears whereas an experienced social worker or psychologist may feel that a certain level or manifestation of distress is 'normal'. This issue points to the need for adequate psychosocial screening by pediatric psychologists pre-admission and during the acute phase of SCT, in order to target those parents most in need for psychosocial guidance and intervention.

Family functioning, an area of increasing importance in the pediatric psychology literature, is still understudied in parents of children undergoing SCT. The experience of fathers is another area of neglect. In many studies on parental stress of parents of pediatric cancer patients, higher stress levels have been found for mothers than for fathers [40], but recent research has shown that the experience of the child's illness often is as stressful for fathers as for mothers [26]. This finding points to the need to include fathers in future studies.

Strengths of the studies included in our review are the large number of longitudinal designs and multi-centered studies and the majority of studies with 90 participants or more. We have found only a minority of studies in which disease-or context-specific measures were used and this is unfortunate, because SCT is a highly complex treatment with very specific issues to deal with for parents. A combination of generic and disease-specific instruments could further our understanding of parental distress trajectories during the course of the SCT.

Conclusions

The authors conclude that the majority of parents of pediatric SCT patients are resilient, 18 months post-SCT and beyond. The most frequently identified risk factor for parental distress in the longer term is the manner in which the parent is able to handle stress during the acute phase. Parents (mostly mothers) with the most severe stress reactions and fear appraisals during the acute phase, continue to experience heightened levels of anxiety, depressive symptoms, and PTSS later on.

The next step is to develop and systematically examine feasible, limited, brief interventions for sub-clinical manifestations of psychological distress prior to and during the acute phase of SCT in parents who have been identified as 'risk' group. Follow-up care is needed for parents, especially when their child recovers and when control visits to the hospital become less frequent. Intervention research is a growing area in medical psychology and despite the many methodological challenges, efforts should be made to implement and evaluate existing intervention programs in this parent group. This can only be done through sound –SCT-specific- assessment, well-funded (inter)national cooperation, and well-developed study designs. Lastly, the ethical domain of conceiving designed children as donors is an area of interest that deserves be studied in the future, as well as the issue of stress in parents of children who need to undergo more than one stem cell transplantation or whose children suffer from more serious late effects, such as chronic graft-versus-host disease or other health problems.

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Child and parental adaptation to pediatric stem cell transplantation

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Abstract

Goals of work. Allogeneic pediatric stem cell transplantation (SCT) is a very intensive treatment with a high mortality and morbidity. The objectives of this study were to assess the 1) self- and proxy-reported HRQoL compared to a norm group, (2) levels of parenting stress compared to a norm group (3) differences in HRQoL and parenting stress pre and post-SCT and (4) the effect of child age and parenting stress on self and proxy reported HRQOL pre and post-SCT. *Methods.* Pre- and on average 10 months post-SCT, 21 children and adolescents and their parent(s) completed questionnaires on HRQoL and the mothers completed a measure of parenting stress. *Results.* Post-SCT, home functioning, physical functioning and total HRQoL scores were lower than the norm group. We found stable HRQoL scores over time, with the exception of the domain home functioning, which was rated lower post-SCT than pre-SCT. Parents reported lower HRQoL scores than the children pre and post-SCT and younger children experienced better HRQoL than older children. Parenting stress was higher post-SCT than pre-SCT and high levels of parenting stress were predictive of poor parental ratings of child HRQoL post-SCT.
Conclusion. Ongoing psychosocial assessment post-SCT is necessary to target children with a lowered HRQoL and parents who experience elevated parenting stress, who may be in greater need of more supportive care.

Introduction

Children undergoing stem cell transplantation (SCT) are subjected to a far-reaching, life threatening and rare medical procedure, only carried out about 60 times per year in the Netherlands. Even though the transplant procedure has become much more sophisticated and as a consequence mortality rates have decreased [8], SCT still represents a severe stressor for the child and family. SCT is often the last possibility after a long-term treatment. The lengthy hospitalization in isolation, physical discomfort, the uncertainty about the outcome and the fear of death are stressors associated with this treatment [31]. Outcomes may vary from cure (and normality) to chronic graft-versus-host disease (GVHD), relapse, or even death [5,14]. Many SCT survivors report long-term physical sequelae like fatigue [27], growth retardation and impaired pubertal development [4,26], pain [19,26], liver complications and decreased lung functioning [36].

An SCT inevitably has an impact on how physical, emotional and social functioning is perceived by the child and family, in other words, on the health related quality of life (HRQoL). HRQoL can be defined as a combination of the experienced health status (e.g. the assessment by a person of his or her own health functioning), and the affective response to problems with respect to this health status [39]. Most HRQoL research in SCT patients has been conducted with adults. In the majority of the studies a negative impact on the HRQoL evaluation in a proportion of adults has been found [8,10,38], often due to functional limitations and somatic symptoms [8] and to concerns about relapsing [2].

However, an extensive review of studies involving pediatric patients [41] showed that the majority of both children and their parents indicated an improved HRQoL with time [5], rated the child's HRQoL as 'good' post-SCT [18,19,26] or even reported a high quality of life post-SCT [3,28]. The reported high HRQoL scores in these studies could be explained in terms of 'response shift': as a result of health changes, an individual may undergo changes in internal standards, values or the conceptualization of HRQoL [35]. Children undergoing SCT might use response shift as a coping mechanism to accommodate themselves to their disease and health status. Furthermore, children with serious illness such as cancer or sickle cell anaemia have been found to show a remarkable 'hardiness' and a lack of psychopathology despite multiple challenges [29].

Differences between self-reported and parent proxy-reported HRQoL have been addressed by several authors (e.g. [9,11,15,39]). Parent-child agreement seems to be influenced by the child's age, with older age predicting greater differences, health status (a higher agreement has been found between parents and chronically sick children than between parents and healthy children), the types of the HRQoL domains investigated

(i.e. a higher agreement for physical aspects of health versus emotional aspects) [11,13], parental quality of life [16] and maternal affective disturbances [5,12]. To our knowledge, the influence of parenting stress on proxy-rated HRQoL has not been studied so far.

The current study was designed to assess 1) self- and proxy-reported HRQoL compared to a norm group, (2) levels of parenting stress compared to a norm group (3) differences in HRQoL and parenting stress pre and post-SCT and (4) the effect of child age and parenting stress on self and proxy reported HRQOL pre and post-SCT.

Patients and methods

Study Design and Procedure

The study had a prospective design pretest (i.e. pre admission for SCT) and posttest. All consecutive patients receiving SCT in the Leiden University Medical Center (LUMC) from February 2004 to May 2005 and their parents were eligible for the study. Excluded were patients younger than three years old and patients and parents who did not speak Dutch sufficiently to fill in the questionnaires. After informed consent was obtained from parents and children older than 8 years, they were asked to complete a booklet of self-report questionnaires at home two weeks prior to admission to SCT.

At least 2 months post-SCT, letters were sent to children and parents briefly describing the follow-up study asking them to complete the same questionnaires again, supervised during a home visit. The Ethical Committee and the Department of Pediatrics of the LUMC approved the study.

Measures

Dutch Children's AZL/TNO Quality of Life Questionnaire (DUX25) [21]. This generic questionnaire was used to asses how children evaluate HRQoL in their day-to-day functioning. There are four domains: family -, physical -, emotional - and social functioning. Besides, a total HRQoL score can be obtained. An example of an item is: "I often feel...." Answers can be given on a 5 point Likert-scale, visualized as smiley's ranging from very happy to very sad (score 5-1). Items scores are converted to a 1-100 scale, with higher scores representing a higher quality of life. The DUX 25 consists of a child form (CF) and a parent form (PF). Both forms were found to be sufficiently internally consistent (i.e. reliable) in this sample (CF: α = .74-.90, PF: α = .79-.88). Scores were compared with a norm group drawn from the total pool of 935 children aged 8-18 [20].

The reason we chose the DUX 25 is that this instrument is user-friendly (because of the smiley's and the limited length of the questionnaire) and because it measures the *affective* appraisal of daily functioning instead of solely assessing functional status, like many other QOL-measures do.

Parenting Stress Index (PSI). The Dutch version of the PSI [1], named NOSI [7] was used to measure parenting stress. The PSI consists of 123 items tapping child and parent characteristics. Child characteristics are measured in 6 subscales, e.g. distractibility/ hyperactivity, adaptability, positive reinforcement, demanding, mood and acceptability. Parent characteristics are measured in 7 subscales, i.e. competence, social isolation, attachment, health, role restriction, depression and marital relationship. Validity and reliability of the PSI are sufficient. The PSI has been used extensively to assess the parent-child dyad in a variety of clinical and research settings e.g. [40]. Because the PSI is a lengthy questionnaire, we asked only one parent (i.e. the mother) to fill it in. The reliability of the total scale in this study was .96.

Demographic and disease related characteristics. Age at first measurement, gender, ethnicity, disease-related characteristics, length of time since SCT and the indication of SCT/diagnosis were obtained from the children's medical files. Parental age and gender were recorded as well.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 14 was used for all analyses. One-way ANOVA was used to compare HRQoL scores to a norm group. We expected HRQoL of patients to be comparable to the norm group post-SCT. Analyses of Variance for Repeated Measures and Tukey Post Hoc correction were applied to compare pre- and post HRQoL scores. Independent T-tests were used to compare HRQoL and parenting stress scores to norm groups. Pearson correlations were used for the associations between the child- and proxy evaluations of HRQoL and to examine the association of age and length of time passed since SCT with post HRQoL. T-tests were also applied to investigate the role of length of time since SCT. Furthermore, Pearson correlations were used for finding associations between parenting stress and pre and post proxy HRQoL reports. Overall, significance was set at α of 0.05. We accounted for multiple testing by using the Bonferroni correction.

Results

Participants

In the study period of fourteen months, 37 pediatric stem cell transplantations were carried out in the LUMC. Of the 28 eligible families approached, 24 agreed to participate (86%). Two families refused to participate because they felt 'too overwhelmed'. Two non-native speaking parents refused participation because of language problems not foreseen by the research team. Three children did not want to fill in the questionnaires, but their parents did. The children (N=21), of which 18 were male (85%) were diagnosed with a variety of malignant (N=13) and non-malignant (N= 8) diseases. The average age of the children pre-SCT was 11 years. See Table 1. Non-participants did not differ from participants with respect to age, gender and primary diagnosis. However, non-Dutch speakers were overrepresented in this group (57% versus 10%) and this might have influenced our results.

Pre-SCT: Two patients were too ill to complete the questionnaires and four children were too young to complete the questionnaires themselves, but their parents filled in the questionnaires. In total 15 children and 31 parents of 21 children (19 mothers and 12 fathers) completed the measures pre-SCT.

Post-SCT (range 2 to 16 months post-SCT, mean 10 months, SD 4.7): Due to a tight time schedule of the research students involved in the project, the study had to take place in a limited period of time. This has resulted in a relatively large variability in time since SCT between the participants. Between the pre-SCT and post-SCT assessment, three patients out of the total 21 potential participants died. The parents of these children were not asked to participate in the follow up assessment. One of the patients could not participate in the follow-up study due to medical complications. One family was lost to follow up. In total 16 children and 31 parents of 21 children (19 mothers and 12 fathers) completed the assessment measures post-SCT. Fourteen children filled in the questionnaires both pre and post-SCT. Because of the low number of girls in our study group and since boys and girls did not differ in age, time since SCT and severity of complications during and post-SCT, they were analyzed as one group.

Health related quality of life of pediatric SCT-patients norm group

Compared to the -age and gender matched- norm group of healthy children (self-report) pre-SCT, HRQoL scores were comparable on all domains. However post-SCT, self-reported HRQoL was significantly lower on the domains Physical Functioning [F (1, 44) = 2.284; p = .027], Home Functioning [F (1, 45) = 2.40; p = .03] and Total HRQoL [F (1, 43) = 2.18; p = .035] (see Figure 1). Compared to the norm group, parents of SCT patients rated their child's HRQoL significantly lower on all four domains and on total HRQoL.

Table 1. Descriptive information of the study sample

Patient characteristics (n=21)	*Mean*	*SD*	*Range*
Age at first assessment (years)	11	4,8	3,7- 18,9
Time since SCT (months)	10	4.4	2-16
	n	%	
Sex			
Male	18	85	
Country of origin			
Dutch	19	90	
Non-Dutch	2	10	
Diagnoses			
Malignant:			
Leukemia (AML, ALL)	9	43	
Non-malignant:			
Blood disease (SAA, MDS)	10	47	
Immune disease (SCID)	2	10	
Parent characteristics (n=31)			
Age at first assessment (years)	42	5.5	35-59
Sex			
Male	12	39	

SCT = Stem cell transplantation; AML = Acute Myeloid Leukemia; ALL = Acute Lymphoblastic Leukemia; SAA = Severe Aplastic Anemia; MDS = Myeloid Dysplastic Syndrome; SCID = Severe Combined Immune Deficiency syndrome.

Figure 1 HRQoL Pre and Post-SCT
Lower scores refer to lower HRQoL

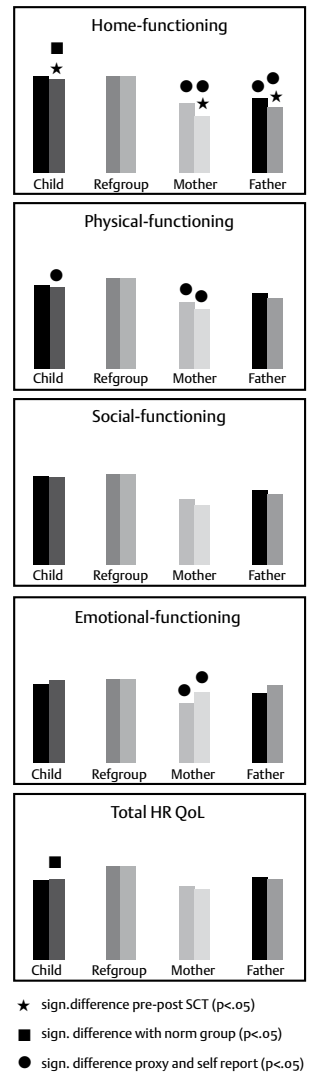

Table 2 Parenting stress scores (mothers) pre and post-SCT

PSI subscales	Pre-SCT Mean (sd) n=13	Post-SCT Mean (Sd) n=19	Norm group n=161
Distractibility	33.3 (7.2)	32.5 (7.5)	30.6 (11.0)
Adaptability	28.1 (6.8)	28.4 (10.8)	32.3 (8.6)
Reinforces parent	19.2 (3.6)	22.0 (5.6)	17.3 (5.2)
Demanding	21.5 (9.3)	25.7 (13.6)*	20.8 (7.3)
Mood	20.1 (5.4)	22.8 (8.8)	21.7 (7.6)
Acceptance	18.9 (5.7)	22.3 (8.8)	22.6 (7.6)
Competence	33.2 (7.8)	**34. 2 (7.3)***	29.4 (9.1)
Social isolation	10.2 (4.0)	12.5 (10.6)	13.5 (6.8)
Attachment	10.4 (3.5)	10.3 (4.1)	12.3 (4.3)
Health	13.1 (5.7)	14.8 (6.7)	13.6 (5.0)
Role restriction	15.5 (6.5)	16.5 (7.4)	14.3 (5.8)
Depression	23.1 (10.4)	24.8 (10.9)	26.8 (9.6)
Marital relation	13.6 (6.1)	13.7 (6.5)	13.5 (6.8)
Total PSI	259.8 (67.1)	277.3 (89.1)*	266.5 (66.9)

PSI, Parenting Stress Index. Higher scores refer to more problems.
* = < 0.05. Printed in bold: sign. difference with norm group; underlined: sign. difference between pre and post-SCT.

Table 3. Bivariate correlations between independent variables with proxy-reported HRQoL pre and post-SCT

	HRQoL Pre-SCT n =13		HRQoL Post-SCT *n=21*	
	r	*p*	*r*	*p*
Demographics				
Time since SCT	-	-	.26	n.s.
Child age	-.47*	.02	.17	n.s.
PSI subscales (mothers)				
Distractibility	.32	n.s.	-.45*	n.s.
Adaptability	-.33	n.s.	-.64*	.01
Reinforces parent	.03	n.s.	-.61*	.01
Demanding	-.56*	.04	-.71*	.01
Mood	-.35	n.s.	-.71*	.01
Acceptance	-.22	n.s.	-.67*	.01
Competence	-.37	n.s.	-.51*	.02
Social isolation	-.48	n.s.	-.33	n.s.
Attachment	-.21	n.s.	-.41	n.s.
Health	. 01	n.s.	-.58*	.01
Role restriction	-.10	n.s.	-.61*	.01
Depression	-.30	n.s.	-.64*	.01
Marital relation	.03	n.s.	-.64*	.01
Total parenting stress	-.34	n.s.	-.38	n.s.

* = <0.05. *n.s.* = not significant

Pre- and post HRQoL scores

There was an effect of time for Home Functioning (i.e. the perception of the child's well-being at home) [F (1, 24) = 6.22; p = .02]. The child-, mother- and father- ratings of Home Functioning post-SCT were lower than the ratings of Home Functioning pre-SCT (see Figure 1). The evaluation of Physical Functioning, Emotional Functioning and Social Functioning remained stable, just as the total HRQoL scores (see Figure 1).

Child-proxy (parent) agreement

There was an effect of group (child, mother) for Physical Functioning [*F* (2, 24) = 3.79; *p* = .04], Home Functioning [*F* (1, 24) = 10.74; *p* = .001] and Emotional Functioning [*F* (1, 24) = 4.03; *p* = .03]. Mothers reported lower scores than the children on all three domains (see Figure 1), whereas the ratings of the fathers only differed with the child ratings on the Home Functioning domain. Mothers and fathers did not differ significantly in their HRQoL-ratings.

Parenting stress compared to the norm group

Compared to the norm group of the PSI, mothers reported to have higher parenting stress levels than parents of healthy children post-SCT, but not pre-SCT. Significantly lower scores compared to the norm group was seen post-SCT on the subscale 'Competence' (the feelings of competence the parent gets from parenting this child). Scores on the other scales were not statistically different from the norm group. See table 2.

Pre- and post parenting stress scores

Thirteen mothers completed the PSI both pre and post-SCT. Most of the PSI domains remained stable over time. However, the subscale 'Demanding' and Total parenting stress were significantly higher post-SCT than pre-SCT, meaning stress accumulated over time (Table 2).

Child age

The age of the children at first measurement was associated with the children's self-reported HRQoL pre-SCT: younger children reported higher HRQoL scores [Pearson correlation coefficient = -.55; p=.03]. Pre-SCT, child age was also associated with proxy-reported HRQoL [Pearson correlation coefficient = -.47; p=.02] (see Table 3). Post-SCT, child age was not associated with self or proxy reported HRQoL.

The impact of parenting stress on proxy-reported HRQoL

The PSI subscale 'Demanding' was significantly related to pre and post proxy HRQoL reports. No other domains of the PSI were correlated to pre-SCT proxy HRQoL report. However, post-SCT, Pearson correlations revealed significant associations between several domains of parenting stress and HRQoL: low adaptability, a lack of positive reinforcement, mood swings, problems related to acceptance, feeling incompetent as a parent, parents' own health, role restriction, parental depressive feelings and dissatisfaction with the marital relationship were all associated with lower proxy-reported HRQoL scores (see Table 3). Strangely, there was no association between total parenting stress and proxy-ratings of HRQoL post-SCT.

Discussion

On average ten months after stem cell transplantation, children and adolescents reported low HRQoL scores compared to a norm group of healthy peers, especially with relation to functioning at home. Parents rated their children's HRQoL significantly lower both pre and post-SCT compared to the children themselves and compared to a norm group of healthy peers. As expected and in line with other studies [31,32], younger children experienced better HRQoL than older children and adolescents. Total parenting stress levels were significantly higher post-SCT than pre-SCT. An important predictor of proxy-rated HRQoL was found in the child's demandingness perceived by the parents, assessed before and after admittance for SCT.

The low post-SCT HRQoL ratings we found are in contrast with results reported in several other studies [5,14,26], in which an improved HRQoL was found after 6 months or more. One explanation for this difference could be the number of assessments done in some of these studies [14,32]. Multiple assessments can generate higher scores: being involved in a trial can create a 'Hawthorne effect' because of the extra attention that is given to a person [6]. Another explanation for the discrepancy could be the length of time passed since transplantation. We assessed HRQoL on average 10 months post-SCT, which is still a more or less active treatment period, whereas other researchers reported improved HRQoL [18] using an interval of three years [38] or five years post transplantation [10]. It is possible that our follow-up period post-SCT was too short to detect any time effects and needs to be extended in further studies.

Differences in child and proxy-evaluations of HRQoL have been reported by many other researchers [9,13,30]. A first explanation could be that parent- and child reports of HRQoL are based on different perspectives: the child reports on his or her subjective personal situation, whereas parents can only infer from observations and communication with the child [22]. Secondly, children are usually more focused on 'here and now', whereas parents are more concerned with their child's well-being and HRQoL in the future [15]. This generates different perspectives on the same issues.

Furthermore, parental emotional functioning and the way parents perceive stressors associated with a child's SCT may negatively affect the evaluations of their child's HRQoL [12,31]. Research has shown that parents of children undergoing SCT can suffer from posttraumatic stress symptoms [24,25] depression [5], distress [33,37] and anxiety [5,24]. Maternal post-SCT anxiety and depression scores have been found to correlate with their children's quality of life ratings at 6 months post-SCT [5]. It has been suggested that maternal psychological problems could be a result of their children's ongoing medical problems and subsequent reduced quality of life. However, the opposite could also be true: parents who experience more stress could be less optimistic in general

and tend to see their children's situation in their own frame of mind [15].

In our study, parenting stress was significantly related to the appreciation of the child's HRQoL, both pre and –especially- post-SCT. Specifically, pre-SCT, the degree to which parents perceived the child to be demanding (e.g. crying, clinging, asking for help) influenced parental HRQoL ratings. Post-SCT, significant associations were found between child demandingness, parental health, role restriction, a lack of reinforcement from the child and marital stress on the one hand and proxy-rated HRQoL on the other. Parents felt significantly less competent than parents of healthy children, post-SCT. This may indicate that post-SCT; parents are faced with more stress concerning parent-child interaction and marital functioning, than pre-SCT. The strain of caring for the child after discharge adds to the already present stressors of parents. Furthermore, the fear of relapse remains and makes parents vulnerable to stress and could be reflected in the lower rating of the domain 'home functioning' by both parents and children, post-SCT. Given the strong relationship between maternal ratings of the child's functioning with ratings of her own functioning, ideally dyadic ratings of both parents and children should be used as much as possible to determine pediatric HRQoL in clinical settings [13,34].

The present study has a number of limitations that should be taken into account. Since our single centre study sample contained a relatively small number of children and parents, there is a chance of missing important relationships or of detecting significant differences even though they may not exist. Due to high mortality and morbidity rates in this patient group, it is very difficult to collect large samples, especially in a country as small as the Netherlands. In addition, our group of children contained more boys than girls and our parent group contained more mothers than fathers. We analyzed fathers and mothers of the same children together, which can cause bias. We only assessed parenting stress in mothers, which limits the generalization of results to all parents. Furthermore, there was a large variance in age and length of time since SCT within the child group. Comparing children with heterogeneous underlying diagnoses (malignant or non-malignant) can also have disadvantages. A recent study by Löf et al. [23] showed that parents of children with leukemia rated their child's HRQoL lower than parents of children transplanted for non-malignant diseases. Children with leukemia reported more problems in the psychosocial area than children with non-malignant diseases.

Due to the small number of participants, we were unable to study other important factors that are of influence on HRQoL, such as clinical factors (primary diagnosis, risk of relapse at SCT, post-transplant complications including acute and chronic GVHD) and socio-demographic characteristics of the participants. Finally, we assessed HRQoL and parenting stress with generic questionnaires. Making use of disease-related and/ or disease-specific questionnaires could provide more specific insight in the effects of SCT on the child's HRQoL and on parental stress.

Other areas of interest like self-esteem and parental quality of life could also be studied with the use of more specific instruments.

Conclusions

Since SCT is of very low incidence and morbidity and mortality rates are high, research involving multiple institutions should be the primary setting for studying patients that are homogeneous with regard to age, diagnosis, time since SCT and the presence of late effects like GVHD. Larger time intervals and multiple assessments are needed to study the process of HRQoL and parenting stress in time in more depth. Proxy data can provide significantly different information than self-reported data, especially for adolescents [9,17], hence consulting the child's own perception next to the parent's view when measuring HRQoL is necessary [13].

We strongly recommend ongoing psychological assessment pre- and post-SCT, in order to target children who report lowered HRQoL scores pre-SCT and/or post-SCT and parents who experience high levels of parenting stress, who may be in greater need of preventive interventions or more supportive care, not only during the active SCT phase, but also in the months following discharge.

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Parental stress and perceived vulnerability five and ten years after pediatric SCT

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Abstract

Goals of work. The aim of the article was to evaluate parental stress, well-being and perceptions of child vulnerability, 5 and 10 years post the stem cell transplantation (SCT) of their child. *Methods.* Seventy-three parents of children and adolescents (mean age 14 years) who underwent SCT 5 or 10 years ago responded to questionnaires on general distress (GHQ), disease-related stress (PIP-SF) and perceptions of child vulnerability (CVS). *Results.* Mean general distress scores were comparable to the reference groups, but 40% of the mothers 5 years post-SCT and 21% of the parents 10 yr post-SCT reported increased stress levels as compared to the reference group. Disease-related stress was comparable to the comparison group of parents of children just off cancer treatment, 5 years post-SCT. Ten years post-SCT, scores were lower than the comparison group. Perceived child vulnerability was high in parents of SCT survivors, compared to parents of healthy children: more than 75% of all parents scored above the cut off point. Perceived vulnerability was found to be a predictor for parental disease-related stress (R^2 .57 for mothers and .63 for fathers).

Conclusions. Although most parents of SCT survivors are resilient, the majority of parents perceive their child to be much more vulnerable than parents of healthy children. These perceptions are associated with disease-related stress and may induce overprotective parenting.

Introduction

With increased survival after stem cell transplantation (SCT), attention has shifted to long-term psychological effects of SCT on survivors and their parents. Even if treatment has been successful, there is a risk of recurrence, acute or chronic graft-versus-host disease (GVHD) and late effects such as pulmonary disease, growth problems, infertility and secondary malignancies [2,12,13]. Previous research has shown that pre-SCT and during the acute phase of SCT, many parents report heightened anxiety, depressive symptoms, parenting stress and general distress, which subsides in the majority of parents between 3 and 12 months post-SCT [16,18,19,26]. Most studies have focused on parental stress and adjustment pre-SCT, during the acute phase and 12-18 months post-SCT. To our knowledge, only one –qualitative- study [6] focused on long term parental distress. Results showed that parents, 4-8 years post transplantation, still worried about late effects of treatment, the risk of secondary malignancies, infertility and their child's psychosocial well-being.

Perceptions of child vulnerability can be found in parent of children with a life-threatening illness [22]. Perceived vulnerability reflects parental attitudes or beliefs that their child is particularly vulnerable or susceptible to harm [23]. It can lead to overprotective behavior in parents and psychological problems in children, such as separation anxiety, psychosomatic complaints, impaired peer relationships and poor school results [23]. In a sample of parents of children with cancer, perceived vulnerability was found to predict child emotional adaptation (i.e. anxiety, depression) [3]. Perceived vulnerability has not been studied in parents of SCT survivors, yet.

One of the variables influencing SCT-related parental stress is socio-economic status (SES): parents from lower SES experienced higher distress throughout the SCT process [18]. Furthermore, younger mothers reported higher levels of distress than older mothers [15]. Time since SCT has been associated with parental distress: the more time elapsed since SCT, the lower the stress levels [18]. The effect of objective medical factors on parental stress levels seems to be small [4,5,19]; the subjective appraisal of these factors seems to be more predictive of parental distress. Differences between parents of children with a malignant versus a non-malignant disease have not been reported, so far.

The aims of our study were to 1) evaluate both general and disease-related parental stress and the perceived vulnerability of the child, compared with population norms, in parents whose child underwent SCT 5 or 10 years ago, 2) compare stress levels of fathers and mothers 5 and 10 years post-SCT and 3) identify which variables determine long-term parental stress post-SCT. Therefore, distress was determined with both medical and socio-demographic determinants as well as with the vulnerability perception of the parents.

Method

Procedure

The Medical Ethical Committee of the Leiden University Medical Center (LUMC) granted approval for this study. All parents of surviving children who underwent allogeneic SCT in the period 2002-2003 (5 years ago) and the period 1997-1998 (10 years ago) in the LUMC received written information about the study and were invited by letter to participate in the study, provided they had sufficient knowledge of the Dutch language. It was explained to the parents that the researchers aimed to evaluate parental stress and well-being, 5 and 10 years post-SCT. When parents gave their written consent (by returning the consent form to the researchers), they received the questionnaire booklets by mail. Parents who did not return their consent form were called to remind them and were given more information about the study, if necessary. Parents were instructed to fill in the questionnaires separately and not to consult each other. After completion of the questionnaires the parents returned the booklets by mail. Several follow-up telephone calls were placed to remind parents to fill in and return the booklets.

Measures

The *Pediatric Inventory for Parents, short form (PIP-SF)* is derived from the 42-item self-report questionnaire PIP that measures parental stress related to the serious illness of their child [21]. Each of the 15 items is rated on two 5-point scales. Parents need to respond to the items twice: the first scale assesses the Frequency of each stressor; the second scale assesses how Difficult the issue has been for the parent. Parents are asked to consider last week when responding to each item. Adequate internal consistency (α =.80-.96) and construct validity of the original and translated version of the PIP have been reported and PIP total scores have been found to correlate significantly with a general non-illness specific measure of state anxiety and parenting stress [21,25]. The original reference group of the PIP consisted of 139 parents whose child was still on treatment and 35 parents (20 mothers, 15 fathers) of children who had recently completed treatment. We decided to use this latter subgroup of parents for comparison with our sample. The PIP-SF was developed by the authors and consists of the 15 items of the full PIP with the highest item-total correlations and the highest clinical relevance. The PIP-SF Total correlated highly with both PIP-SF Frequency and PIP-SF Difficulty (.95 and .93 respectively) in our sample, hence we decided to use the PIP-SF Total scale, only. Internal consistency of the PIP-SF in our sample was .95. See the Appendix for the items of the PIP-SF.

The *General Health Questionnaire (GHQ)* 12-item version is a self-report measure of non psychotic psychiatric disorders that can be used as a general measure for psychological distress. The psychometric properties of the Dutch version of the scale are reported to be highly satisfactory [10] and the questionnaire has been used frequently in both research and clinical settings [24,27]. The cut-off score of the GHQ is 2, meaning a total score of 0 or 1 is interpreted as 'no psychological morbidity' and a score of 2 or higher is interpreted as 'possible psychopathology'. Internal consistency in our sample was consistent with previous reports (α was .86).

The *Child Vulnerability Scale (CVS)* [8] is an instrument to identify parental perceptions of their child's vulnerability. It contains 8 items with a 4-point response scale ranging from 'definitely false' to 'definitely true' scored from 0 to 3. Items include statements as 'In general, my child seems less healthy than other children'. The proposed cut-off score for the CVS is 10. The Dutch version of the CVS is available [20] and it has good reliability and validity, but the results of this study have not been published, yet. Therefore, the American reference group was used in this study [8]. Internal consistency for the current sample was .88.

Demographic and clinical information

Gender, age, marital status, educational level of the parent, as well as gender and age of the target child, the child's underlying diagnosis and the number of years since SCT were retrieved from the medical files. See Table 1.

Statistical analysis

Differences between responders and non-responders were calculated with the use of independent T-tests and chi square tests for non-parametric variables. We used Cronbach alphas to determine the reliability of our measures. One sample T-tests were performed to compare the two study groups with reference groups on general distress and perceived vulnerability. Independent T-tests were used to compare disease-related stress with available data from the subgroup of parents of children who were off cancer treatment (N=35) [25]. To determine whether the percentage of fathers and mothers scoring above a cut-off score differs significantly from the percentage of people in the reference group, we used a one-sample chi square test. Independent T-tests were performed to compare the two study groups with regards to general and disease-related stress and perceived vulnerability. All analyses were conducted for mothers and fathers, separately.

Our study groups were relatively small, hence only a limited number of variables could be included in the regression analysis. Therefore a pre-selection of the three highest correlating predictors was made. If not significant, we still added them into the model for continuity. Predictors were situational characteristics (parent age, originally Dutch (yes/no) and medical characteristics (time since SCT (in years) and malignant disease (yes/no)) per outcome subscale (total disease-related stress and general distress). Perceived vulnerability served both as an outcome and as a possible predictor for disease-related and

general stress. We accepted r > .30 as an arbitrary criterion for the selection of the variable. The analyses were performed separately for mothers and fathers, because dependence exists between the data. A combination of the most strongly related variables was entered simultaneously in the regression analysis. Firstly, the model was carried out for perceived vulnerability (CVS). Next, the model was carried out for the disease-related (PIP-SF) total score and for general stress (GHQ). For each regression analysis, the explained variance (*R square*) was determined, and it was tested using the *F*-test. T-values and their significance levels were calculated to test the hypothesis whether the contribution (the regression coefficient (*B*)) of an entered variable significantly differed from zero.

Results

Participants

In the group of 28 eligible pairs of parents 5 years post-SCT, five couples refused. Reasons for refusal were: not motivated to participate, did not want to be reminded of the SCT period, too busy with work and the fact that the SCT had been too long ago. Eight families did not return their booklets even after repeated reminders by mail and by phone. The final sample 5 years post-SCT consisted of 29 parents (15 mothers and 14 fathers) of 15 survivors, the response rate was 54%. In the group of parents 10 years post-SCT, eligible parents of 54 SCT survivors were approached. Eight families refused to participate. Three of the returned booklets were blank and were excluded and 18 families did not return their booklets. The final sample 10 years post-SCT consisted of 25 families (46% response rate), comprised of 23 mothers and 21 fathers. See Figure 1.

Non-responders consisted of significantly more non-Dutch parents (37% in the group of parents 5 years post-SCT and 21% in the group of parents 10 years post-SCT) compared to 13% and 8% percent, respectively, in the participant groups. Non-Dutch parents were defined as parents who were born outside the Netherlands. Parents in our study group were born in the following countries: Morocco, Turkey, Aruba and Surinam. The children of non-responders did not differ from the children of participating parents with respect to age and diagnosis (i.e. the percentage of malignant diagnoses). In total, parents of 82 eligible survivors were approached by letter and 73 parents (49%) consented, consisting of 38 mothers and 35 fathers. For a detailed description of the total study group, see Table 1.

Figure 1. Flow chart of participants

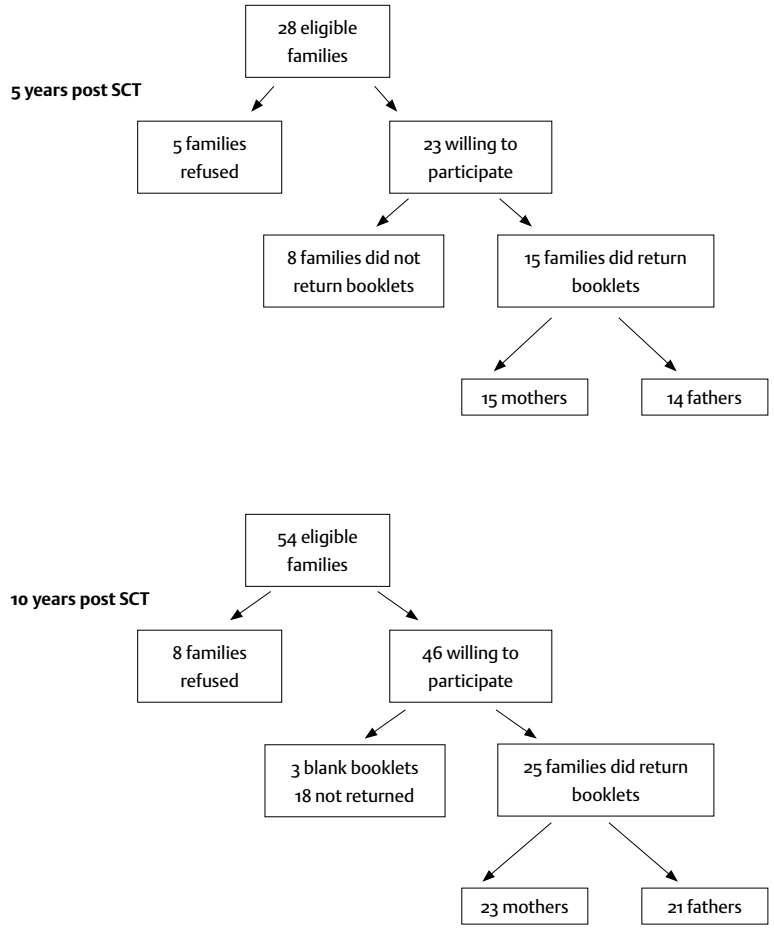

Table 1. Descriptive information about study participants and their children

Factor	*5 years post SCT (29)* *Mean (sd)*	*10 years post SCT (44)* *Mean (sd)*
Parent age (years)	44.7 (4.7) Range 37-58	46.3 (5.5) Range 39-63
	N (%)	N (%)
Parent gender		
Female	15 (55)	23 (48)
Parental education		
Primary school only	3 (10)	6 (14)
High school only	6 (21)	9 (21)
MBO	10 (35)	9 (21)
HBO	4 (14)	14 (31)
University degree	5 (17)	2 (4)
Unknown	1 (3)	4 (9)
Country of origin		
Dutch (The Netherlands)	25 (86)	36 (82)
Other	4 (14)	8 (18)
Child age (years)	13.4 (4.8) Range 5-22	16.6 (4.4) Range 11-26
Child gender		
Female	9 (53)	10 (40)
Male	8 (47)	15 (60)
	N (%)	N (%)
Diagnosis child		
ALL, AML, CML,JMML	8 (48)	14 (56)
MDS	-	3 (12)
Immune deficiency	2 (12)	1 (4)
Fanconi anemia	3 (18)	-
Other blood diseases	-	5 (20)
Metabolic disorders	-	1 (4)
X-LPD	2 (12)	-
Other diseases	2 (12)	1 (4)

MBO, Post high school education, community college level; HBO, College level;
ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; X-LPD, X-linked lymphoprolerative disorder

Parental stress

Scores on the disease-related measure were comparable in mothers and fathers, 5 years post-SCT, compared to parents of children off treatment for cancer [25] (fathers T = 1.73, $p > .01$; mothers T = .9, $p > .01$). Scores of parents 10 years post-SCT were significantly lower than the comparison group (fathers T = 3.62, $p < .01$; mothers T = 3.20, $p < .01$).

The items of the PIP-SF with the highest scores were: '*Seeing my child sad or scared*', '*Feeling helpless over my child's condition*', '*Feeling uncertain about the future*' and '*Feeling scared that my child could get very sick or die*'. About 20% of all parents rated these situations as 'very difficult' or 'extremely difficult'.

Results on the general stress measure revealed that 10 years post-SCT, mothers and fathers did not show elevated levels of general distress, compared to population norms of the instrument (i.e. men and women in the same age group as the participants): mean scores were comparable and 24% of the parents scored above the cut-of score versus 26% in the general Dutch population with comparable ages [10]. However, one sample chi square tests showed that in the group of parents 5 years post-SCT, the percentage of mothers scoring above the cut-off (44%) was significantly higher than the percentage of women in the reference group (26%), $p < .05$.

Scores on the CVS revealed that both mothers and fathers 5 and 10 years post-SCT perceived their child to be much more vulnerable than parents of healthy children in the American community-based reference group of parents [8]. The percentage of parents with scores above the cut-off was 94 % for the group 5 years post-SCT and 76% for the group 10 years post-SCT, as opposed to 10.1 %. Mothers and fathers scored equally high. See Table 2.

Table 2. Parental stress scores of study groups and reference groups: means and standard deviations for mothers and fathers

Outcome measure	5 years post-SCT Mean (sd)	10 years post-SCT Mean (sd)	Reference group Mean (sd)
	Mothers		
	(N=15)	(N=23)	
PIP-SF Total	66.4 (28.7)	55.4 (25.6) [a,b]	74.4 (24.0)
GHQ	2.2 (3.1)	1.4 (2.2)	1.8 (0.8)
CVS	18.7 (7.6) [a]	16.2 (8.0) [a,b]	2.1 (2.5)
	Fathers		
	(N=14)	(N=21)	
PIP-SF Total	55.4 (25.6)	42.6 (15.6) [a]	69.2 (23.6)
GHQ	1.4 (2.2)	1.6 (2.2)	1.3 (0.3)
CVS	18.3 (8.0) [a]	16.2 (3.7) [a,b]	2.1 (2.4)

PIP-SF, Pediatric Inventory for Parents, short form; GHQ, General Health Questionnaire; CVS, Child Vulnerability Scale. [a] significant difference with reference group, [b] significant difference between 5 and 10 years post SCT

Differences between stress levels 5 and 10 years post-SCT

General parental stress of mothers and fathers 5 years post-SCT did not differ significantly from parents 10 years post-SCT (GHQ T = .34, *p* = .74). Perceived vulnerability was significantly higher, 5 years post SCT (CVS fathers T = 9.71, *p* =.004, CVS mothers T = 6.27, *p* =.02*)* and disease-related stress was significantly higher in mothers 5 years post-SCT (PIP-SF T = 2.52, *p*<.05) than in mothers 10 years post-SCT. For fathers, scores did not differ (PIP-SF T = 1.49, *p* =.16).

One sample chi square tests showed that in the group of parents 5 years post-SCT, the percentage of parents scoring above the cut-off (40%) on the GHQ was significantly higher than the percentage in the group 10 years post-SCT (21%). The same holds true for the percentage of parents scoring above the cut off on the CVS: 94% in the group 5 years post-SCT was significantly higher than 76% in the group 10 years post-SCT. Separate analyses for fathers and mothers reveal the following percentages above the cut off: fathers go from 92% (5 years) to 69% (10 years) and mothers go from 98% to 78%.

Correlates predictors of parental stress and perceived vulnerability

To assess the influence of time since SCT, ethnicity, underlying disease (malignant versus non-malignant) and parent age on parental stress and perceived vulnerability, we calculated Pearson correlations for mothers and fathers separately. The results are depicted in Table 3. We found that, for mothers, disease-related stress was significantly correlated with ethnicity and underlying disease. General stress and perceived vulnerability were also correlated with ethnicity. For fathers, older age was correlated with higher disease-related stress. Perceived vulnerability was correlated with ethnicity, underlying disease and paternal age. Comparisons between fathers and mothers showed that age was of influence for disease-related stress (.58) and perceived vulnerability (r .42) in fathers, but not in mothers (.13 and -.06 respectively). For mothers, whether the underlying disease of the child was malignant was significantly correlated with disease-related stress (.43). The correlation was not significant for fathers.

Predictors of perceived vulnerability and parental stress

Forced entered regression analyses, performed separately for mothers and fathers, showed that the variation in perceived vulnerability was explained by a combination of three of the following (highest correlating) variables: time since SCT, ethnicity, underlying disease and parent age. For mothers, the adjusted R^2 of the combined predictors was somewhat lower than for fathers, but this difference was not significant (.30 versus .35). Time since SCT was not predictive of perceived vulnerability.

Forced entered regression analyses showed that perceived vulnerability (CVS levels) accounted for 57% of the variance in disease-related stress (PIP-SF) in mothers and 63% in fathers. Parental age was predictive of perceived vulnerability in fathers, but not in mothers. Perceived vulnerability did not predict general stress (GHQ) for mothers or fathers. See Table 4.

Table 3. Correlation matrix between parental stress, perceived vulnerability and influencing variables for mothers (N=38) and fathers (N=35)

	PIP-SF total	GHQ	CVS	Time since SCT	Ethnicity	Malignant/non-malignant	Parent age
			Mothers				
PIP-SF total	-	.44*	-.71**	.36	.56*	.43*	.13
GHQ		-	-.21	.08	.42**	.07	.02
CVS			-	-.16	-.59**	-.20	-06
Time since SCT				-	-.04	-.04	.15
Ethnicity					-	.28	-.17
Malignant/non-malignant disease						-	.0
Parent age							-
			Fathers				
PIP-SF total	-	.36	-.77**	.33	.39	.27	.58
GHQ		-	-.24	.01	.30	.09	.17
CVS			-	-.15	-.47**	.33*	-.42
Time since SCT				-	-.01	-.08	.10
Ethnicity					-	.18	.04
Malignant/non-malignant disease						-	.12
Parent age							-

* correlation is significant at the 0.05 level, * correlation is significant at the 0.01 level

PIP-SF, Pediatric Inventory for Parents, short form; GHQ, General Health Questionnaire; CVS, Child Vulnerabili

Table 4. Simultaneous Regressions (Beta) for Measures of Adjustment[1]

	CVS	PIP-SF total	GHQ
	Mothers		
Adjusted R square (sign. of F)	.30*	.56**	.07
Parent age			-.09
Time Since SCT	.09		
Ethnicity (yes/no)	.56**	.15	.22
Malignant (yes/no)	-.08	.20	
CVS	-	-.57**	-.07
	Fathers		
	CVS	PIP-SF total	GHQ
Adjusted R square (sign. of F)	.35**	.66**	.07
Parent age	-.32	-.30*	-.13
Time since SCT			
Ethnicity (yes/no)	-.39**	-.02	.06
Malignant (yes/no)	-.25		
CVS	-	-.63**	-.27

[1]values reported are standardised regression coefficients (Beta) with significance of *t*, with the exception of the rows presenting *Adjusted R squares* with significance of *F*. * $p < 0.05$ ** $p < 0.01$
CVS = Child Vulnerability Scale; PIP-SF= Pediatric Inventory for Parents, short form; GHQ = General Health Questionnaire

Discussion

Having a child who needs to undergo stem cell transplantation is a stressful event for any parent. Our study revealed that, ten years after SCT, most parents have reached normal levels of general distress and disease-related stress, compared to the reference groups. However, five years post-SCT, 40% of the mothers still score above the cut-off score on the general stress measure. Five years post-SCT, disease-related stress was comparable to parents of children who had recently ended cancer treatment, both in mothers and in fathers. Furthermore, a large percentage of all parents (more than 75%) in our study group still perceive their child to be much more vulnerable than other children. This finding is understandable, given the life-threatening illness of their child in the past, the intensive and stressful SCT-procedure their child had to undergo and the possible late effects.

Regression analyses showed that perceived vulnerability was predicted primarily by ethnicity; underlying disease, time since SCT and parent age played a minor role. High perceived vulnerability could be a reflection or result of chronic strain or even burnout in parents of SCT survivors. In a recent study among parents of brain tumor survivors -a group of survivors with possible sequelae, just like SCT-survivors-, more than half of the mothers reported to have burnout symptoms, consisting of emotional exhaustion, physical fatigue and cognitive difficulties [17]. Strain does not have to be traumatic or severe to have high psychological impact. Even low-intensity stressors may create a severe effect, if they are long-lasting or recurrent [17].

Parental disease-related stress was predicted primarily by perceived vulnerability and paternal (not maternal) age. Furthermore, even though the percentage of non-Dutch parents was low in our sample, we found a significant correlation of ethnicity with disease-related stress and perceptions of child vulnerability. Parents from an ethnic minority have reported higher general stress levels before in different illness populations [9], possibly due to a lack of resources and social support. For mothers, underlying disease (malignant or not) was related to disease-related stress. For fathers, whether the underlying disease was malignant or not was related to perceived vulnerability. Parents of children with a malignant disease are usually faced with more stress before SCT than parents of children with a non-malignant disease, due to lengthy periods of treatment with chemotherapy and -in many cases- having to deal with the shock of a relapsed disease. These prior illness experiences influence parental stress levels during and after the SCT trajectory [19]. Furthermore, it has been found that post-SCT, the psychosocial impact of late effects is higher in children with a malignant disease [14]. The child's health post-SCT is found to have a significant impact on parental emotional functioning [7]. Furthermore, the fear of another relapse, sometimes referred to as the Damocles syndrome' [1,11], can be present in both cancer survivors and their parents for a long time.

Limitations of the present study are the relatively low number of participants and, more specifically, the low response rate. Because of the variety in reasons for non-participation, it is difficult to tell whether this leads to under- or over reporting of parental stress levels. The manner in which the study was conducted, namely by mail only, can lead one to speculate that only the families that were doing well responded and therefore that the study might not be representative of this population. It is not easy to conduct research with families for whom SCT has taken place so long ago, because some parents want to put the whole experience behind them and others feel that it is no longer relevant to report on their own well-being after so many years. Furthermore, the study was single-centered, meaning results are more difficult to generalize to other medical centers. We did manage to include a large percentage of fathers in our study.

Lastly, although disease-related measures can render important information on the reactions of parents to the specific situations that having an ill child might bring, a major limitation of these instruments is the lack of an adequate comparison group, since these measures have not been used in a population of parents of healthy children. In the present study, we compared our findings on the disease-related measure (PIP-SF) with a group of Dutch parents whose children had just come off treatment for cancer, knowing that there are differences between the two groups regarding the frequency of hospital visits and worries about immediate and late effects of treatment. Furthermore, the present study group also consisted of parents whose children had a non-malignant disease. However, we did find that the perceived difficulty of some of the disease-related situations (mostly worrying about the child's health and future) is still relatively high in a subset of parents of SCT patients.

The authors conclude that most parents of SCT survivors are resilient and do not report heightened stress scores, compared to reference groups. Mothers are more prone to general stress, 5 years post-SCT. Perceptions of child vulnerability are high in this group of parents and this could lead to overprotective parenting behavior. We recommend more in-depth qualitative studies on the experiences of parents who are from another cultural background and long term psychosocial screening in parents of SCT survivors who are at risk for long term stress, alongside with the existing late effects clinics. Post-SCT care could involve group counseling and referrals to individual counseling in the parents' own environment if necessary.

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Appendix. Item-total and item-scale correlations of the PIP short form scales

Items	Corrected Item-Total Correlation Frequency	Corrected Item-Total Correlation Difficulty
1 (5)*. Being unable to go to work/job	.61	.56
2 (7). Speaking with doctor	.65	.40
3 (13). Being with my child during medical procedures	.72	.59
4 (16). Seeing my child sad or scared	.72	.62
5 (17). Talking with the nurse	.63	.66
6 (18). Making decisions about medical care or medicines	.62	.41
7 (25). Having little time to take care of my own needs	.71	.55
8 (26). Feeling helpless over my child's condition	.69	.49
9 (28). Handling changes in my child's daily medical routines	.58	.53
10 (29). Feeling uncertain about the future	.70	.59
11 (30). Being in the hospital over weekends/holidays	.69	.64
12 (33). Helping my child with medical procedures (e.g. giving shots, swallowing medicine, changing dressing)	.61	.56
13 (36). Feeling scared that my child could get very sick or die	.65	.40
14 (38). Watching my child during medical visits/procedures	.72	.59
15 (42). Spending a great deal of time in unfamiliar settings	.72	.62

*The numbers between brackets refer to the item numbers in the original questionnaire.

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Health-Related Quality of Life, Cognitive Functioning and Behavior Problems in Children with Langerhans Cell Histiocytosis

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Abstract

Goals of work. This study was designed to evaluate generic and disease-specific health-related quality of life (HRQoL), cognitive functioning and behavior problems of children with Langerhans Cell Histiocytosis (LCH). Furthermore, we investigated which medical determinants and social demographic factors were predictive for HRQoL, cognitive functioning and behavioral problems. *Methods.* In this cross-sectional case-control study 24 children ranging from 7 to 17 years of age were administered a HRQoL questionnaire, cognitive tests and behavior ratings. In addition, a disease-specific HRQoL measure was developed and tested. Results were compared to a reference group consisting of healthy peers and to proxy-ratings by parents and teachers. *Results.* Children with LCH reported a lower physical HRQoL than the reference group ($p \leq .05$). Children older than 12 reported lower HRQoL scores. Scores on the disease-specific HRQoL questionnaire were lower than on the generic measure used. Performances on cognitive tests varied widely, short term visual memory was most affected. Twenty-five percent of the children follow special education. According to parents and teachers, children with LCH had more internalizing behavior problems (i.e. anxiety and depression), compared to the instrument norms. Children with Diabetes Insipidus, other CNS involvement and children who have had chemotherapy had more cognitive and behavior problems than the other children with LCH. *Conclusions.* HRQoL is affected in children with LCH, especially in older children. Children with LCH show more internalizing problem behavior than their peers. Teachers are important additional informants about behavior problems.

Introduction

Langerhans Cell Histiocytosis (LCH) is a rare non-malignant disease that can manifest itself in diverse ways. It is the result of an abnormal proliferation of pathologic Langerhans cells, accompanied by other inflammatory cells in various tissues. The lesions are destructive, and healing results in scarring and fibrosis [3,23]. Symptoms can range from a single bone lesion to a life threatening multi-system disorder. The peak onset of LCH is between 1 and 4 years, although it can occur at any age [8]. Children may suffer from severe consequences of the LCH. The highest incidence (20%) of Central Nervous System (CNS) disease is the involvement of the posterior pituitary, resulting in Diabetes Insipidus (DI) [32]. Besides this endocrinopathy, other neurological CNS-related sequalae are reported as well, although at a lower incidence: ataxia, physical problems, neuropsychological problems and learning difficulties [7,11,23,24]. LCH-treatment depends on the extent of the disease. Localised disease might be treated with local therapy, including the application of corticosteroids or surgical curettage. In case of disseminated LCH, chemotherapy is often the backbone of treatment [2,12].

In a large retrospective survey, neurological sequelae were found in 11 percent of 182 children with LCH [11]. Some of these became apparent years after diagnosis, with the latest reported after 14 years. Cognitive deficits have been reported in subgroups of pediatric LCH patients [21]. The first cohort-study on cognitive outcome in children with LCH was done by Nanduri et al. [23] who reported intellectual deficits (IQ's below 85) in 11 of 38 children (39%), eight of the 11 children showed evidence of CNS involvement.

Whether health related quality of life (HRQoL) of children with LCH is affected in the long-term is still a matter of debate. HRQoL is defined as the subjective response to situations in daily life [10]. One of the few studies on HRQoL of children with LCH showed that the domain 'emotional functioning' was most often affected [24]. Lau et al. [20] found no differences with healthy peers in a large retrospective study of patients with 'only' bone lesions using generic questionnaires. However, in another study more than 50% patients with multi-system disease LCH [24] reported an adversely affected HRQoL. Most research has relied on generic HRQoL measures, but these instruments lack the sensitivity to assess areas of functioning important to children with a specific illness [22]. For LCH, no disease-specific measures have been developed. Behavior problems in children with LCH have been reported as well: a wide range of behavioral and/ or psychological problems were reported in 27.5 % of long-term survivors of pediatric LCH, namely: varying combinations of depression, anti-social behavior and difficulties with inter-personal relationships [24].

Most sequelae were found in children in whom multiple organ systems were involved [11,24] and children with CNS involvement [23,24,32]. So far it is unclear whether impairments in cognitive functioning are caused by LCH or by its treatment. Chemotherapy

is a common treatment for children with LCH and a recent meta-analysis by Campbell et al. in this journal [4] has shown that contemporary treatment for acute lymphocytic leukemia causes neurocognitive deficits. Of course, dosage varies between the illnesses and there are other contributing factors that need to be taken into account.

Considering the neurological and psychological consequences as well as the physical complaints described, the present study aimed to answer the following questions: (1) Does HRQoL of children with LCH differ from a norm group of healthy children? (2) What disease-specific consequences do children and parents report about LHC? (3) What are the cognitive deficits and behavior problems?

Methods

Patients

All eligible members of the Dutch LCH family association who have a child (8-18 years) with LCH were approached by letter about the study. Twenty-four families agreed to participate and were contacted by phone and visited by one of the authors (VMK). During this visit, informed consent forms were signed, patient characteristics were registered and questionnaires and tests were administered to the children. Parents completed their questionnaires in a separate room. Teachers of the children received the questionnaire by mail. In total 24 children were included, 16 boys and 8 girls. Teachers of twenty-two children participated in the study (two could not be contacted). The percentage of children visiting special education schools is 25 % (High for the Netherlands, normally 3-5 %). They visit schools for children with learning problems, schools for speech and hearing problems and schools linked to a rehabilitation center. These six children all had CNS-involvement. For a detailed description of the study group, see Table 1.

Table 1. Description of LCH Study Group

No.	Sex /Age (years)	System involved	Age at diagnosis (years)	Duration treatment (years)	Years since end treatment	CNS Involve-ment	DI	Chemo therapy	Permanent consequences
1	M /10	Skin, Pituitary, GI, Liver *	2	3	5	+	+	+	Growth hormone deficiency, vision problems
2	F / 16	Pituitary	15	1	0	-	+	-	Fluid balance problems
3	M / 9	Bone	4	3	2	-	-	-	Muscle pains
4	M /11	Bone, Skin	2	9	0	-	-	+	Hearing problems
5	M / 9	Bone, Liver *	.9	1	0	-	-	+	Back pain
6	F / 12	Bone	3	8	1	-	-	+	Headache, fatigue
7	M / 17	Bone, Pituitary, Skin	1	1	15	+	+	+	-
8	M / 11	Skin	.6	10	1	-	-	-	-
9	F / 10	Bone	1	2	7	-	-	+	Obesity
10	M /10	Bone	9	0.5	1	-	-	-	-
11	M / 10	Bone, Lymph nodes, GI	4	0.5	6	-	-	-	-
12	M / 13	Skin	1	0.3	12	-	-	-	Lung-, bladder- and ear infections
13	F / 10	Bone, Skin	.3	0.5	9	-	-	+	-
14	F / 10	Bone, Skin	3	7	1	-	+	+	Wheezing, does not go outside
15	M / 16	Bone, Sinuses, Mouth	2	2	13	+	-	+	Behavior problems
16	M / 9	Bone	6	0.5	3	-	+	+	Skin problems
17	F / 7	Bone, Skin, GI	.9	1	7	-	+	+	Vaginal discharge, fatigue
18	M / 14	Bone, Brain *	2	1	12	+	+	+	Infections of ear, bronchia & teeth. Headaches
19	M / 13	Bone, Skin, Mouth, Liver, Kidney *	.1	7	6	-	-	+	Headaches
20	M / 8	Bone	1	0.5	7	-	-	+	-
21	F / 16	Bone	16	1	0	-	-	+	Fatigue, obstipation, infections
22	M / 9	Bone, Skin	1	1	8	-	-	-	Bumps on the skull
23	M / 11	Bone, Lymph nodes	8	1	3	-	-	-	-
24	M / 10	Bone, Skin, GI, Brain *	.4	3	7	+	+	+	Growth hormone deficiency, obesity
	M 11.9 SD 2.9		M 3.4 SD 4.5	M 2.7 SD 3.0	M 3.4 SD 3.2	+ 5 (20.8%)	+ 8 (33.3%)	+ 16 (66.7%)	

CNS, Central Nervous System; DI, Diabetes Insipidus; GI, gastro-intestinal; * Risk organs

Measures

Dutch Children's AZL/TNO Quality of Life Questionnaire (DUX 25) [16]. This questionnaire was used to asses how children evaluate HRQoL in their day-to-day functioning. There are four domains: family, physical, emotional and social functioning plus a total HRQoL score. Item are formulated as: "I often feel...." Answers can be given on a 5 point Likert-scale, visualized as smiley's ranging from very happy to very sad. Items scores are converted to a 1-100 scale, with higher scores representing a higher quality of life. The DUX 25 consists of a child form (CF) and a parent form (PF). Both forms were found to be sufficiently internally consistent (i.e., reliable) in this sample (CF: α = .74-.90, PF: α = .79-.88. Values between .7 and. 8 are considered good). Scores were compared with a norm group of 935 healthy peers stratified by age [15].

*LCH-specific Quality of life Questionnaire (LCH DUX)***.** This disease-specific questionnaire was developed to look for the effects of the disorder on the daily lives of the patients and their families. Item lists were developed from clinical experience (RME), literature search and parent interviews (IvdL). A team of researchers (HMK, VK, AMK) collaborated on item development. Items were reviewed and discussed by the other team members to ensure appropriateness. Questions were adjusted accordingly. The disease-specific LCH DUX contains 22 items (see appendix). The instrument has a similar lay-out as the DUX 25, also with a child (CF) and parent (PF) form. Items are scored identically on a 1-5 scale and converted to a 1-100 scale, with higher scores representing better HRQoL.

We found good reliability for the child and parent forms (Cronbach's α = .73 and α = .85 respectively).

Wechsler Intelligence Scale for Children- Third Edition (WISC-III nl) [18,31]. Four subtests of the WISC-III were administered to estimate cognitive functioning: Arithmetic, Coding, Information and Digit span. Results were compared to Dutch norm groups [18]. Raw cognition scores were standardized into reference scores with a mean of 103. A child was considered to score "below average" on a subtest when the score was one standard deviation or more below the mean.

Child Behavior Check List 6-18 (CBCL), Youth Self Report (YSR), Teacher Report Form (TRF) [1]. Three parallel questionnaires (standardized Dutch versions [28-30]) were used to assess the presence of behavior problems. Parents completed the CBCL, children (13 years and older, 14 in total) filled in the YSR and the teachers were sent the TRF. Informants had to rate 112 items on how true each item for the child is: 0 = not true; 1= somewhat or sometimes true; 2 = very or often true. The items on all three questionnaires can be transformed in 3 domains: internalizing problems, externalizing problems and a total score. Results were compared to Dutch norm groups. Problem scores are classified as normal (≤ 85th percentile), borderline clinical (85th-93rd percentile) and clinical (≥ 93rd percentile), for boys and girls separately.

Demographic and disease characteristics. Age, onset of LCH, schooling and sex of the child plus marital status and level of education of the parents were obtained, as well as disease-related characteristics of the children. We recorded time since diagnosis, duration of treatment, time since the end of treatment, location of LCH, whether there was DI, other CNS involvement (defined by us as non-pituitary related issues like ataxia, neuropsychological or learning problems) and whether the children had received chemotherapy. Lastly, we recorded permanent consequences for all patients (Table I).

Statistical Analysis

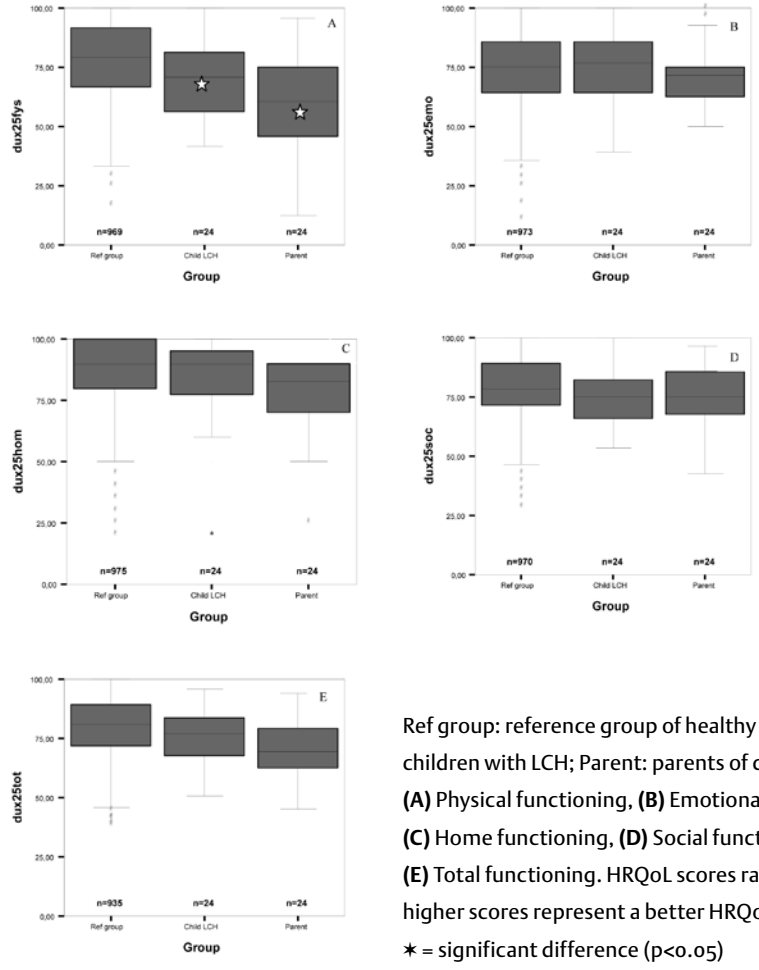
The reliability of the DUX and LCH DUX scales were analyzed with Cronbach's alpha coefficients. Multivariate analysis of variance (MANOVA) was used to compare mean HRQoL scores between children with LCH, a reference group of healthy children and parent ratings. Cognition and behavior scores were compared to norm scores using one sample T-tests. For all analyses an α-value less than 0.05 was required for significance.

Results

Health-related quality of life

Children with LCH reported a significantly lower score ($p < .05$) on the physical domain of the generic HRQoL questionnaire than the reference group, indicating a lower HRQoL concerning their own health and physical appearance. Parents even reported a significantly lower score ($p < .03$) on the physical domain than their children (Figure 1). Scores on the other domains were not statistically different from to the reference group. No differences were found between ratings of parents of children who ended their treatment more or less than 5 years ago, no gender differences and no relations between generic HRQoL and disease characteristics. Children older than 12 showed significantly lower scores on the scales physical functioning (p = 0.001), home functioning (p = 0.019) and total generic HRQoL (p =0.003).

Figure 1. Health-related quality of life (HRQoL)



Ref group: reference group of healthy children; Child LCH: children with LCH; Parent: parents of children with LCH.
(A) Physical functioning, **(B)** Emotional functioning,
(C) Home functioning, **(D)** Social functioning,
(E) Total functioning. HRQoL scores range from 0-100, higher scores represent a better HRQoL .
∗ = significant difference ($p<0.05$)

Compared to generic HRQoL the disease-specific HRQoL scores were low. On the LCH DUX scale parents showed a mean total score of 57 and children scored 59 on average (on the generic DUX 25 scale the mean scores were 71 and 76 respectively). Four items showed scores that were one standard deviation (SD) or more below the total mean score: *Having to take medications I find…*; *Not being able to play with other children makes me feel…; Not being able to go to school because of my LCH is…* and *Compared to other children, I feel…* See the Appendix for the full LCH DUX questionnaire.

Cognitive functioning

Participants showed wide-ranging WISC subtest scores (from 3 SD below (1) to 3 SD above (19) the mean norm score (10). In total 54 % of the children scored one SD or more below average on one or more subtests and 25% on two or more subtests (See Table 2). The subtest *Coding* (visual short-term memory and quick responding) was the most difficult for children with LCH; 38 % of the children scored one SD below the mean on this subtest. The children scored highest on the subtest *Digit Span* (auditory short term memory): 33 % of the children scored one SD above the mean on this subtest.

Table 2. IQ-subtest scores

WISC III-NL Subtest	**Norm score* Mean (SD)**	**-1 SD N (%)**
Information (general factual knowledge & long-term memory)	9.8 (3.7)	6 (25)
Coding (visual motor coordination, speed & concentration)	8.3 (3.2)	9 (38)
Arithmetic (attention, concentration & numerical reasoning	9.7 (3.1)	6 (25)
Digit Span (short-term auditory memory & concentration)	12.1 (4.4)	4 (17)
Number of subtests ≤ 1 SD	**N (%)**	
0 subtest	11 (46)	
1 subtest	7 (29)	
2 subtests	2 (8)	
3 subtests	4 (17)	

WISC III-NL, Wechsler Intelligence Scale for Children, Dutch version;
* Norm scores range from 0-20, the average score lies between 7 and 13.

Behavior problems

Teachers reported three times and parents reported twice as many problems as the children. Compared to the norm groups of healthy peers, the rates of internalizing behavior problems (i.e. anxious and depressive behavior) in children with LCH were significantly higher, according to both parents and teachers. Total problems reported by the parents in the LCH group were significantly higher than the control group. Children self-reported behavior problems were not statistically different from the control group. However, the percentage of children with LCH scoring above the 93rd percentile (clinical range) compared to the norm groups was larger in various scales, e.g., self-reported externalizing behavior (See Table 3).

Table 3. Problem behavior reported by children, parents and teachers

	Parents (N=24) (CBCL)		**Teachers (N=22) (TRF)**		**Children (N=14) (YSR)**	
	Mean (SD)	Clinical N (%)	Mean (SD)	Clinical N (%)	Mean (SD)	Clinical N (%)
Internalising behavior						
Sample	10.17 (8.2) *	9 **(30)**	9.8 (9.7) *	7 **(32)**	10.4 (5.1)	1 (7)
Norm group	4.5 (4.3)	7	5.0 (5.6)	7	8.4 (5.5)	7
Externalising behavior						
Sample	6.6 (5.3)	1 (4)	7.3 (10.2)	4 **(17)**	11.0 (7.1)	2 **(14)**
Norm group	8,2 (6.3)	7	6.7 (8.4)	7	11.2 (6.4)	7
Total problems						
Sample	31.5 (20.4) *	4 **(14)**	32.4 (29.1)	5 **(23)**	30.4 (13.8)	0 (0)
Norm group	21.3 (14)	7	21.9 (21.4)	7	32.8 (16.3)	7

CBCL, Child Behavior Checklist; TRF, Teachers Report Form; YSR, Youth Self Report; * Significant difference with the norm group ($p \leq .05$); Clinical, scores above the 93rd percentile; Significant differences with the norm group ($p \leq .05$) are printed in bold.

Discussion

This study evaluated both generic and specific HRQoL in children with LCH as well as cognitive functioning, (teacher and parent rated) behavior problems and disease characteristics. Considering the severity of LCH, generic HRQoL scores evaluating emotional, social and home functioning were comparable to reference groups of healthy peers. Children with LCH did report a significantly lower HRQoL regarding their physical functioning, compared to the norm group. This is in line with HRQoL research in pediatric oncology: children with bone tumors and their parents report more problems in physical

functioning than a healthy control group [17]. As previous research in other illness groups has shown [9,15], older children with LCH report a lower HRQoL, possibly due to a growing consciousness about their disease.

The LCH DUX disease-specific questionnaire showed lower scores than the generic measure. It seems that children with a chronic illness, when asked in general how they think they are doing, tend to 'leave out' their illness and report relatively high HRQoL scores. It is unclear if this generic 'not including the illness process' happens unconsciously or results from repressive adaptation, as described in children with cancer [25] or if 'response shift' takes place: as a result of health state changes, an individual may undergo changes in internal standards, values or the conceptualisation of HRQoL [26,27] and as a consequence, may report a higher HRQoL than expected. When children are approached directly about their illness experiences in a disease-specific questionnaire, they are forced to focus on difficulties they might come across because of their illness.

Teachers reported by far the most behavior problems compared to parents or children with LCH. According to the answers of teachers and parents, children with LCH showed more internalizing behavior problems (anxiety, depression) than norm groups. Discrepancies between self-report and parent proxy-report have been documented in other illness groups before: parents tend to underestimate their child's HRQoL [5,9]. Many researchers have noted that parents and teachers frequently disagree on their assessment of behavioral/emotional problems in children [14,19]. Such differences do not mean that either reporter is inaccurate, because parents and teachers see the child in different situations and their ratings may be affected by many different factors [13].

While interpreting the results of this study, limitations should be kept in mind. To shorten the total assessment time per child, only four subtests of the intelligence test were used to assess cognition, which only generates a general indication of cognitive functioning. Furthermore, the heterogeneity of the study group with respect to age, time since diagnosis and disease characteristics, combined with the relatively small sample size, limited the choice of statistical analyses. All children being members of the Dutch LCH Family Association, also may have introduced a bias. Lastly, due to the small sample size we were unable to evaluate all psychometric qualities of the new HRQoL instrument. This is one of our future aims.

It is recommended that future studies in this area are longitudinal in design and aim to enhance sample size, preferably through international studies including the involvement of the Histiocyte Society. Effort should be made to enable children with LCH to participate and to live 'normal lives' as much as possible, with the aid of parents, teachers and multidisciplinary hospital staff. Additionally, a 'buddy' or peer might be helpful as a model figure.

Involving teachers as informants of child behavior offers another frame of reference and enables the gathering of more objective information. The newly developed LCH-specific questionnaire might be a first start to come to a common language to study HRQoL in this group of patients, analogue to the tool for assessing disease activity, developed by Donadieu et al.[6]. Lastly, considering the behavioral and cognitive problems experienced by a large percentage of children with LCH, more thorough and longer psychosocial follow-up assessment and care is needed.

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Items and scores of the LHC DUX

	Item	Mean score *
1.	Having to take medications, I find…	35**
2.	Not being able to play with other children makes me feel…	15**
3.	Giving a class presentation about ICD is…	56
4.	How the doctors speak with me, I find…	58
5.	How my parents deal with my LCH, I think is…	70
6.	Doing what the doctor says I find…	52
7.	About my LCH I often feel…	45
8.	Not being able to go to school because of my LCH is…	21**
9.	Compared to other children, I feel…	29**
10.	Talking about LCH with other children I find…	41
11.	Taking medication in front of others I find…	46
12.	Later, when I'll be older, my LCH will be…	67
13.	Going to the hospital is…	44
14.	When I am visiting someone I feel…	85
15.	At this moment I think about my LCH as…	48
16.	What I know about LCH is…	56
17.	Explaining LCH to others is…	41
18.	At school my LCH is…	72
19.	At home my LCH is…	74
20.	Doing sports for me is…	72
21.	Taking a rest in the daytime is…	46
22.	Having to do everything on time is…	56
Total score LCH DUX child form		**59 (SD 14)**

* Scores range from 0-100, a higher score means a higher quality of life; **
1 SD or more below the total mean score

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8

Summary and discussion of the results

Summary and discussion of the results

Parental reactions to childhood cancer

The diagnosis and treatment of cancer in one's child can cause long-lasting psychological effects in a parent. The review article in Chapter 2 shows that feelings of uncertainty, anxiety, depressive symptoms and posttraumatic stress symptoms (PTSS) are most prevalent shortly after the parents are confronted with the diagnosis of childhood cancer. These emotional manifestations of strain decrease to near normal levels over time in the majority of the parents. This means that most parents are resilient even when confronted with the stressors of long and intensive cancer treatment, possible medical complications and the omnipresent fear of losing one's child. A subgroup of parents reports ongoing stress, even many years post-treatment. As is often found in the general population, mothers tend to report more and higher levels of symptoms than fathers with respect to anxiety, depression and PTSS. The following risk factors for long lasting parental distress have been identified in previous research: pre-existing psychological problems, high trait anxiety, low social economic status and financial worries, child behavior problems, high perceived care-giving demands and less perceived social support [1,11]. Certain coping strategies, such as active problem solving, seeking social support and optimism can serve as protective factors [10,20].

One of the problems with pediatric psychology research is the variety of definitions of the core elements of the psychological stress process that are used, often described together and simply referred to as 'stress'. It is important to clarify what is meant by 'stress' and to specify the temporal course of a stressor [16]. Furthermore, the existing assessment instruments may fail to assess the specific problems that parents of cancer patients have to deal with [9]. There is a risk of "pathologizing" parental adaptation to childhood illness, which can have negative effects such as increased stigma and a de-emphasis on parents' daily functioning [25].

One way of addressing this problem is to carefully select assessment instruments that capture the broad ray of challenges parents of children with a life-threatening disease are confronted with. The study of the psychometric properties of the Dutch version of an American disease-related measure (Chapter 3) was an effort to describe parental stress in terms of the frequency of illness related events and the perceived difficulty of these events, thereby doing justice to the specificity of the experiences of parents. Parents of 107 children diagnosed less than 18 months ago with cancer in three different academic medical centers were included in this study. Eighty percent of the children were still on treatment. Risk factors for high disease-related stress were female gender, paternal age (older fathers reported significantly more distress than younger fathers) and child age (parents of younger children reported higher stress scores than parents of older children).

Furthermore, as was expected, parents of children on treatment had significantly higher stress scores than parents whose children had completed treatment. Parents of children diagnosed more recently reported more stress than parents of children who were diagnosed longer ago. Surprisingly, the perceived difficulty of the stressors did not decline over time. This finding means that although the frequency of disease-related events is diminished with time, parents still perceive these events as difficult.

Alongside the PIP, three other questionnaires were administered, which measured state and trait anxiety, general stress and stress associated with parenting (parenting stress). A high correlation was found between scores on the PIP and on the first two measures, but a low correlation was found with the measure of parenting stress. This means that disease-related stress has an important overlap with anxiety (or worrying about one's child) and stress in general but less with stress associated with disciplining one's child. Disease-related stress however adds to clarify the specific stressors for parents of very ill children, especially during the period of active treatment: frequent hospital visits and admissions, waiting for news from the doctor, watching one's child undergo medical procedures can all add to the stress. These issues are not included in 'generic' questionnaires.

Parental reactions to stem cell transplantation (SCT)

As described in the review study in Chapter 4, the majority of parents of pediatric SCT patients appear to be resilient, 18 months post-SCT and beyond. The process of SCT is comprised of several phases and distress levels seem most elevated in the pre-SCT phase and the acute phase during hospitalization, but can stay elevated after discharge. The most frequently identified risk factor for parental distress in the longer term is the way the parent is able to handle stress during the acute phase. Parents (mostly mothers) with the most severe stress reactions and fear appraisals during the acute phase, continue to experience heightened levels of anxiety, depressive symptoms and PTSS later on [4,18]. This finding points to the significance of the state-trait model of anxiety in this context: parents with highest pre-existing anxiety (trait) and parents with the most severe anxiety reactions during the acute phase (state) are most at risk. Certain maternal coping strategies, such as acceptance, humor, putting reason before emotion and having positive cognitive appraisals during the acute phase have been identified as protective factors, e.g. [5].

The longitudinal study (Chapter 5) on parenting stress and child- and parent rated health related quality of life (HRQoL) demonstrated that 31 parents rated their children's HRQoL significantly lower both before and on average ten months after SCT than the 21 children themselves. Total parenting stress levels were significantly higher post-SCT than pre-SCT. An important predictor of proxy-rated HRQoL was found in the

Table 1. Overview of studies presented in this thesis

	Review article Stress reactions of parents of pediatric cancer patients Chapter 2	Cross sectional study PIP: Psychometric qualities, parents of children with cancer Chapter 3	Review article Stress reactions of parents of SCT patients Chapter 4	Longitudinal study Stress of parents and HRQoL of children pre-post-SCT Chapter 5	Cross sectional study Stress reactions of parents 5/10 years post-SCT Chapter 6	Cross sectional study Sequelae in children with LCH Chapter 7
Participants/ Number of articles	n = 67 articles	n = 100 mothers, n = 74 fathers	n = 18 articles	n = 19 mothers n = 12 fathers n = 21 children	n = 38 mothers n = 35 fathers	n = 24 children
Characteristics of the children	Children with cancer	Children diagnosed with cancer 1-18 moths ago (80% on treatment), mean age 9.6	Children who underwent SCT	Children who underwent SCT with heterogeneous diagnoses. Mean age at first assessment 11.0	Children who underwent SCT 5 or 10 years ago with miscellaneous diagnoses. Mean ages 13.4 and 16.6 v	Children with LCH. 21% CNS involvement, 30 % Diabetes Mellitus, 67% chemotherapy. Mean age 11.9
Assessment instruments	*n.a.*	PIP, STAI, PSI-SF, GHQ	*n.a.*	DUX 25 (child and parent form), PSI	PIP-SF, GHQ, CVS	DUX 25, LCH-DUX, WISC III subtests, CBCL/TRF/YSR
Outcome	Most emotional stress reactions were reported around diagnosis, i.e. anxiety, depressive symptoms, PTSS and uncertainty. Most parents seem resilient. A subset of parents reports continuing stress.	The Dutch PIP has adequate (test-retest) reliability and validity. Evidence was found for the four-factor model and the one-factor model.	Highest levels of parental stress are reported in the period preceding SCT and during the acute phase of SCT. Stress subsides in the majority of parents 3-6 months post-SCT.	Diminished HRQoL with regards to home functioning, not on other domains. Higher levels of parenting stress, on average 10 months post-SCT. Parents felt less competent as a parent, post-SCT.	40% mothers 5 years post-SCT reported elevated stress levels. High levels of perceived vulnerability: 94% after 5 years, 76% after 10 years for both mothers and fathers.	Lower physical HRQoL More internalizing problems Miscellaneous cognitive problems. Visual short term memory was affected in many children. Special education: 25%
Risk factors	- High levels of stress at diagnosis - Lower SES - Trait anxiety - Child behavior problems - Less perceived social support - Traumatic life events	- Parents of children on treatment - Less time since diagnosis - Higher paternal age - Lower child age	- High levels of stress during SCT - Avoidant coping - Lack of support - Pre-existing stress - Younger maternal age - Lower SES - ICU transfers - Child mood disturbance	- Older children (lower HRQoL) - High perceived child demandingness (higher parenting stress)	- Parents of children with a malignant disease - Higher paternal age - Being non-Dutch - Higher perceived vulnerability	- Older age - Children with Diabetes Insipidus, other CNS involvement and children who have had chemotherapy

child's demandingness perceived by the parents assessed before admittance and on average 10 months post-SCT. Perceived demandingness is a component of parenting stress. It is operationalized as e.g. 'my child demands more attention from me than I can give'. Post-SCT, significant associations were found between (parent-reported) child demandingness, parental health, role restriction (i.e. the manner in which a parent feels restricted by his or her child) and marital stress on the one hand and proxy-rated HRQoL on the other. Parents felt significantly less competent than parents of healthy children, post-SCT. This may indicate that post-SCT parents are faced with more stress concerning parent-child interaction and marital functioning than pre-SCT. The strain of caring for the child after discharge adds to the already present stressors of parents. Furthermore, the fear of relapse remains and makes parents more vulnerable to stress. This could be reflected in the lower rating of the domain 'home functioning' by parents and children, post-SCT. Ten months post-SCT, most children are back in school, the majority of parents have returned to their work place and visits to the clinic have diminished. However, our findings imply that families are still experiencing serious strain in a period of time when others expect them to pick up their old lives and move on. It may mean that parents lack both professional and social support in this phase.

Scant literature has been published on long-term parental stress post-SCT. The only earlier published report was a qualitative (interview-based) study on parents 4-8 years post-SCT [8]. The study described in Chapter 6 showed that general stress levels seemed to return to normal, 5 and 10 years post-SCT in 38 mothers and 35 fathers. Disease-related stress was relatively high 5 years post SCT, but was lower than the comparison group, 10 years post SCT. However, 5 years post-SCT, the percentage of mothers scoring above the cutoff point of general stress was significantly higher than in the reference group. Another finding of this study was that the majority of parents still perceived their child to be extremely vulnerable, both 5 and 10 years post-SCT. Parents from another cultural background reported higher stress scores than parents who were originally Dutch. Perceived vulnerability was higher in parents of children with a malignant disease, a finding that was expected, since these children are objectively more vulnerable. Risk of relapse, secondary malignancies and late effects are more common in this group of children than in children transplanted for a non-malignant disease and the parents of the first group have had more illness related experiences, which are of direct influence on parental distress [23].

Perceived vulnerability

Perceived vulnerability is an important predictor for disease-related parental stress, as was shown in the study on long-term psychosocial consequences of SCT in parents (Chapter 6). Whether high perceived vulnerability leads to overprotective parenting behavior

has not been proven [32], but perceptions of vulnerability do influence child emotional adjustment (i.e. anxiety, depression) negatively [3]. Parental worry, communicated either implicitly or explicitly to a child, may convey that he/she is vulnerable or helpless and thus serves to increase anxiety and/or depression. Whether high perceptions of vulnerability cause psychological or HRQoL related problems in SCT survivors remains an area to be studied.

Assessment of parental stress

Assessment of parental stress reactions shortly after the diagnosis of a life-threatening illness of a child is important to identify those parents or families most in need. Disease-related and disease-specific measures can add important information about parental adaptation to stressful illness related situations. Furthermore, these instruments are more sensitive to change and can help to evaluate the effectiveness of interventions. The assessment measures that were selected for our studies on parental stress were based on availability in the Dutch language, data on reliability and validity and the frequency of use in other (inter)national studies. To study the impact of a life-threatening illness of a child on a parent from different angles, a variety of measures was used, i.e. measures of stress associated with parenting (Parental Stress Index, full and short form), state and trait anxiety (State Trait Anxiety Index), general stress or well-being (General Health Questionnaire) and a measure of perceived child vulnerability (Child Vulnerability Scale).

Because of a lack of disease-related instruments in Dutch, the Pediatric Inventory for Parents (PIP), a disease-related measure of parental stress was translated into Dutch. Results regarding the Dutch version of the PIP were satisfactory [33] and showed that it is possible to make a reliable and valid assessment of the frequency and perceived difficulty of various illness related situations. Reliability scores for the PIP Total scales and three of the four subscales (Medical care, Emotional distress and Role function) were adequate and confirmatory factor analyses showed acceptable fit for the four-factor model. PIP scores correlated strongly with a generic measure of anxiety and general psychological functioning. This means that disease-related distress, although it measures a different construct, can have considerable overlap with general well-being and anxiety. The added value of the PIP, however, is that the instrument assesses parental evaluations of their stress concerning specific disease-related situations, such as '*bringing my child to the hospital*' or '*being in the hospital during weekends and holidays*'. Scores on the PIP could be transformed into an individual 'stress profile', which could be used to tailor psychosocial support.

The low correlation of PIP scores with parenting stress scores suggests that stress resulting from difficulties disciplining and setting limits to one's child (parenting stress) is not the same as stress associated with having a child with a serious illness

(parental stress). However, in various studies, e.g. [12], the PSI is used as a measure of parental stress instead of stress associated with parenting. This strategy might result in drawing the wrong conclusions about the stress reactions parents can have as a result of their child's illness.

Children's reactions to SCT and LCH

Children who have undergone SCT can have a compromised HRQoL, due to late effects and ongoing worries about a relapse or other complications. We found that children and adolescents in our study, when assessed on average 10 months after SCT, reported decreased HRQoL scores in the domains 'home functioning' and total HRQoL. Home functioning refers to items like '*At home, I often feel…*' or '*The things we do together at home, I find…*'. However, scores on the domains emotional, physical and social functioning were comparable to healthy peers. This finding suggests that children, even if they have not completely recovered physically post-SCT, are resilient and display 'hardiness'. They seem less bothered by the aftereffects of the SCT than their parents, possibly because they tend to live more in the 'here and now' and have the desire to return to their old lives. Adolescents are more at risk for a lowered HRQoL than younger children, a finding that is in line with most research in this area e.g. [6]. Older children might be more aware of the limitations and risks post-SCT. Problems related to a lowered 'home-functioning' could refer to the adolescents' desire to be more autonomous than their parents allow them to be. Perceived vulnerability could be an influencing factor and it would be interesting to study the relation between these concepts.

A phenomenon that needs to be taken into account when measuring HRQoL is 'response shift' [26], which refers to a change in the meaning of one's self-evaluation of a target construct as a result of: (a) a change in the respondent's internal standards of measurement; (b) a change in the respondent's values; or (c) a redefinition of the target construct (i.e. reconceptualization) [27]. Response shift could lead SCT- or cancer survivors to rate their HRQoL higher than expected, because they compare themselves to a period of severe suffering and may conclude that they are enjoying a good HRQoL at present [26].

Children with LCH seem to be affected more by the sequelae of their disease than children who underwent SCT, possibly due to detrimental effects on both cognitive and emotional functioning, resulting in lower HRQoL. Furthermore, LCH is an unpredictable illness in both time and severity, which makes it more difficult to cope with.

Assessment of HRQoL in children

HRQoL in pediatric patients can be assessed with generic and disease-related or disease-specific instruments, just like parental stress. To assess HRQoL in children with

Langerhans Cell Hystiocytosis (LCH), a disease-specific questionnaire was developed and used, the LCH DUX (see Chapter 7). This instrument rendered lower HRQoL scores than the generic HRQoL measure. A possible explanation is that children with a chronic illness, when asked in general how they think they are doing, tend to 'leave out' their illness and report relatively high HRQoL scores. It is unclear if this generic 'not including the illness process' happens unconsciously or results from repressive adaptation, as described in children with cancer [24] or if 'response shift' takes place. When children are approached directly about their illness experiences in a disease-specific questionnaire, they are forced to focus on difficulties they might come across because of their illness. Children with LCH appear to have not only a lowered HRQoL, but also cognitive and educational problems (one quarter of our study group is in special education) and more internalising emotional problems than their healthy peers.

Children and adolescents in our longitudinal study (Chapter 5) reported low HRQoL scores compared to a norm group of healthy peers 10 months post-SCT, especially with relation to functioning at home and physical functioning, but also in the total HRQoL score. In the other HRQoL areas (i.e. social functioning and emotional functioning), scores were comparable to the reference group. Parents rated their children's HRQoL significantly lower both pre- and post-SCT compared to the children themselves and compared to a norm group of healthy peers, a finding that has been reported in several other studies [2,7].

Limitations of the studies

Obtaining a sample size large enough to perform sufficient statistical power is a continuous challenge in pediatric oncology research in the Netherlands. The number of newly diagnosed children in our country is not the main problem, but the fact that the 500 newly diagnosed children per year are spread around the country in seven different academic hospitals. Although the number of children undergoing stem cell transplantation have increased substantially, the numbers undergoing transplant at any one center remain relatively small, a factor that has slowed psychosocial research considerably [22]. Multicenter research is to be preferred, but it is far from easy to organize, as experience taught us while undertaking the study on the psychometric qualities of the Pediatric Inventory for Parents [33]. One of the reasons was that all three Medical Ethical Boards of the participating centers needed to give approval, which was a time consuming process. The other reason was that practical matters were more difficult to tackle from a distance, for example handing the forms to the parents when they were in the hospital or outpatients' clinic was more reliable when the research assistant was present. If all Dutch

pediatric cancer patients would be treated in one single center, it would be much easier to conduct large psychosocial studies in this population, in conjunction with medical treatment protocols and during visits to the outpatient's clinics and late effects clinics.

A problem associated with small study groups is the fact that parents of children with different cancer diagnoses often are analyzed together, which was also the case in the studies presented in this thesis. Whether this really is a problem is a matter of debate. As Stein and Jessop have stated, there is more variability within diagnostic groups than between them, hence a non-categorical approach is to be preferred [29,30]. On the other hand, it is conceivable to think that parenting a child with standard risk ALL would be different from parenting a child with a malignant brain tumor or a bone tumor, both during treatment and afterwards, when parents and children have to deal with late effects of treatment. Likewise, parents whose child undergoes SCT once are incomparable to parents whose child needs a second transplantation due to relapse or graft rejection. Parents of children with an underlying malignant disease have different pre-SCT illness experiences than parents of children with a non-malignant disease. These prior illness-related experiences during previous admissions have been found to be predictive of later SCT-related stress [23]. On the other hand, these 'experienced' parents are more used to being in a hospital and dealing with hospital staff and thus might be better equipped to face SCT-related stress during the acute phase, compared to parents without a history of frequent hospital admissions.

Another limitation or challenge is participation. Inviting parents to participate in studies on parental stress while they are still experiencing high levels of distress is not an easy job: parents feel overwhelmed with the burden placed on them by their child's illness and report that any additional request is perceived as 'too much'. Other parents report that they wanted to avoid experiencing intense feelings when confronted with questionnaires about their emotional reactions. This might mean that the parents with highest stress levels did not participate in the study. On the contrary, in studies on long-term psychosocial effects of cancer or stem cell transplantation, parents have answered that they felt 'it was all in the past' and no longer relevant to them. These two phenomena can reflect over- and/or underreporting of stress levels and give different patterns of generalization of the data.

There is a lack of reliable and valid disease-related or disease-specific assessment instruments available to medical and pediatric psychologists [16]. However, using disease-related instruments in clinical practice or research also has its disadvantages, because comparison of results is very difficult, if not impossible. Usually there is no reference group of parents of healthy children available and many instruments have only been used in one illness group. Hence, drawing conclusions based on the results can be difficult and disease-related or disease-specific instruments should always be used together with

generic measures. The development of the PIP [31] has helped to identify and assess areas of strain for parents of seriously ill children. A disadvantage of this disease-related measure is that it seems less useful for the assessment of long-term parental stress, because the disease-related events do no longer occur and thus no longer seem relevant to parents. However, we learned that their worries and concerns do not disappear altogether. It is striking that the short form of the PIP (the PIP-SF, which is comprised of 15 items with the highest item-total correlations and the highest clinical relevance), which was used in the study in Chapter 6, contains items that appear to be centered mainly on worrying about the child and its future. Worrying seems to be an ongoing process and has found to be associated with parental perceptions of child vulnerability. The PIP-SF seems a promising screening tool for disease-related parental distress, but needs further studying.

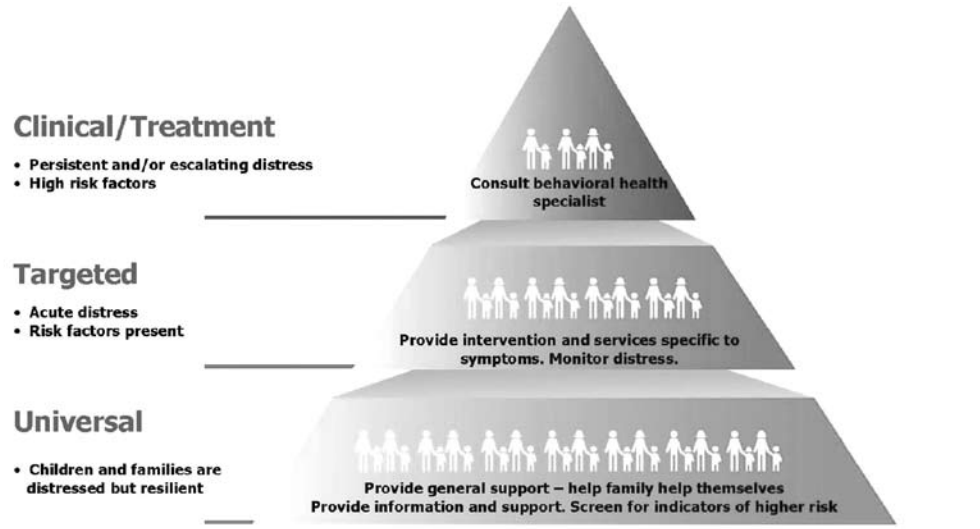
Lastly, data of all of the studies were collected as self-reports, which is the most conventional and convenient method of surveying groups. However, this method of data collection has certain limitations, for example: response style, which may involve either the reluctance to report distress or the tendency to over-report distress. Studies on self-reported distress and parenting stress could contain problems of overlapping concepts and possible underlying personality factors which can contribute to covariation in the assessed variables [19]. Another limitation of this study method has to do with parents from other cultural backgrounds. In all four studies in this thesis, the percentage of non-Dutch parents was low. Language problems seem to be a major cause, but they cannot explain the low rates of participating parents from other cultural backgrounds entirely. It seems that the way most pediatric psychological research is conducted, namely by means of pencil-and-paper self-report questionnaires, does not always match the expectations, preferences or abilities of all eligible parents. It is possible that parents from another cultural background, in which the group is more important than the individual person, perceive questionnaires about how an individual is feeling or coping as less relevant.

Practical implications and directions for future research

Assessment and indication of need

Adequate assessment forms a solid base for both clinical and research purposes. Finding the right assessment instruments to capture the unique experiences of parents of children with a life-threatening disease or children undergoing SCT is a matter of ongoing discussion among pediatric psychologists. All the while, we need to realize that we are dealing with parents who in majority are 'normal', psychologically healthy people, but have suddenly ended up in an abnormal situation. An inspiring model, developed by Anne Kazak, is the Pediatric Preventative Health Model (PPPHM), which builds on the assumption that the majority of families with a child with cancer are competent and adaptively organized families, without any elevations in their *a priori* risk (as a group) for psychopathology [15]. The PPPHM model (Figure 1, published with permission of the original author) divides all families into three categories, based on risk factors and needs.

Figure 1. Pediatric Preventative Health Model



The term *Universal* is used for the largest group of families, who are seen as distressed, but resilient. This category consists of about 50% of all families who are helped with general support, information and preparation to invasive medical procedures by the child life specialist. This universal support is also to prevent more problems in the near future. The term *Targeted* is used to indicate those families at higher risk and in need of services specific to symptoms; about 35% of the families fall into this category. One of the goals of psychosocial services is that these parents do not 'move up' in the pyramid because their problems are accumulating. The smallest category on top of the pyramid (about 15% of the families) refers to *Clinical/Treatment*, to highlight those families at highest risk for persisting and escalating stress, who need to be referred to a behavioral health specialist (e.g. a pediatric psychologist, social worker or psychiatrist).

A model like the PPPHM adequately illustrates the fact that the majority of parents are able to cope with a cancer diagnosis and treatment in their child and do not need extensive psychosocial counseling. The model also has an economic advantage: costly and time consuming specialized psychosocial interventions will be offered only to those parents most in need. However, assessing the parents' level of risk and the specific strengths of the family is not an easy job. There is a need for psychometrically sound measures that are appropriate for use with pediatric health populations and for parents of children undergoing SCT or in treatment for cancer. Parents of children who need to undergo SCT could be screened in the weeks before admittance; parents of children newly diagnosed could be screened starting four weeks after diagnosis. The PIP could be used in its short form as one of the screening methods and state and trait anxiety should also be included as ingredients of screening batteries, since both pre-existing (trait) anxiety and acute anxious reactions (state) to diagnosis and treatment have been identified as risk factors for long-term parental stress. In the SCT-setting, the Prior Illness Experience Scale [23] could be used to assess parental and child experiences with cancer treatment before SCT. It has been shown to be predictive of parental stress during and after SCT. Furthermore, known risk factors such as traumatic life events, pre-existing psychopathology and a lack of support (see Figure 1) should be detected in each family early on in treatment by doctors, psychologists, social workers and nurses.

Timing of assessment seems to be a difficult issue, because, as our review study in Chapter 2 showed [34], studies vary considerably in the choice of time points. In many instances, it matters whether the investigator is interested in processes that occur at the time of disease onset, in the period following initial diagnosis, during the course of treatment, when complications arise (such as a relapse), at the completion of treatment or in the longer term. Pediatric psychology research would benefit from consensus on the optimal points in time to assess emotional reactions in parents following the diagnosis of cancer in their child. Assessment should preferably take place at one, six and 12 months after diagnosis, at the end of treatment and one and/or two years after the cessation of treatment, see Box 1. In this way, the comparison of results from research will be facilitated and patient and parent care will be enhanced. Assessment shortly after diagnosis provides important information on the initial reactions of parents. However, clinical practice has shown that assessment within four weeks after diagnosis is difficult, because parents are often too overwhelmed to take the time to fill in questionnaires. Assessment at six and twelve months post diagnosis will give insight in parental stress over time according to different disease phases. The end of treatment brings new challenges for parents and longer term follow-up is necessary to keep track of the parents who still report high (post-traumatic) stress levels.

Box 1. Timing of psychological assessment

Proposed time points for assessments
- 1 month post diagnosis
- 6 months post diagnosis
- 12 months post diagnosis
- End of treatment
- One/two years after cessation of treatment

In conclusion, it seems necessary to find (or develop) a reliable, easy to use screening tool for all parents and families of pediatric cancer patients that can be used at different time points and that is focused on known risk- and protective factors. Consensus is needed between all seven child cancer centers in the Netherlands about the content and implementation of such an instrument. A likely candidate for this purpose would be a Dutch version of the Psychosocial Assessment Tool (PAT) [13,21], which is a brief screening tool for psychosocial risk in families of children newly diagnosed with cancer. In addition, one could think about developing a semi-structured interview to capture parental stress and risk- and protective factors.

Intervention

Once the target families have been identified, evidence-based, brief and easy to use interventions need to be implemented in daily practice. Most individual counseling will be aimed at parents in the 'Clinical/Treatment' group, whereas parents in the 'Universal' or 'Targeted' group could also profit from group interventions and psycho-educational programs. The results of the study on long-term parental stress show the importance of early detection of parents at risk to prevent high levels of distress which were observed 5 years after SCT.

Hurdles like enrollment/response rate, prevention of drop out, timing and funding of interventions need to be taken collaboratively. Specifically, parents of children undergoing SCT seem to need more specific information and/or psychoeducation before admission, to reduce pre-transplant stress. Issues such as 'how to prepare for the lengthy and stressful admittance period', 'how to obtain adequate support' and 'what emotional reactions can be expected' need to be addressed. For this purpose, a DVD has been developed at the LUMC for parents of children who need to undergo SCT, with the aim to provide practical information and to serve as a coping model. The DVD was based on an existing film as part of an intervention study for parents of newly diagnosed children with

cancer [14,28]. Issues before, during and after SCT are addressed in a group discussion of four families of SCT survivors. Parents receive the DVD approximately 5-6 weeks before admittance and are instructed to watch the DVD at home. They are requested to fill in a short questionnaire on feasibility, acceptability and usefulness of the DVD. For parents in the Universal group of the pyramid, watching the DVD could be sufficient preparation pre-SCT, while parents in the Targeted or Clinical group could perhaps be offered individually tailored sessions pre-SCT. Fragments of the DVD could be watched in these sessions with a psychologist or social worker and discussed with the parents.

During the acute phase of SCT (i.e. Phase II of the Model of Medical Traumatic Stress, see the Introduction Section), support seems to be sufficiently accessible for most of the parents, because they spend most of their time in the clinic and have the access to help and attention from both staff (nurses, physicians, social workers, child life specialists and psychologists) and other parents. The biggest challenge seems to be the period immediately after discharge post-SCT, when parents are facing the burden of caring for their (still ill) child at home and are expected to 'return to normal life'. We need to find a way to be more outreaching to parents in this stage, for example by organizing house visits by child life specialists and/or nurse-practitioners for every family in the first two weeks after discharge post-SCT. More follow-up care should be provided to those parents who suffer from longer term (posttraumatic) stress, i.e. the parents in the upper part of the triangle in Figure 1, by means of referral to local psychosocial health care specialists and/or support groups. The same holds true for parents of children with Langerhans Cell Hystiocytosis, who are largely 'out of sight' of hospital staff once treatment of their child is completed. These parents are burdened with both the care for a child with late effects of the disease and treatment and with their own uncertainty about the future. It would be worthwhile to study the effectiveness of an internet-based intervention and/or peer contact group for these parents.

Considering the adverse effects of childhood cancer treatment, there is a need for disease-specific psychosocial interventions for survivors of childhood cancer. A face-to-face psycho-educational group intervention was developed in the Netherlands, aimed at empowerment of survivors of childhood cancer by teaching disease-related coping skills. The program improved disease-related skills and psychosocial outcomes [17]. E-health developments should be considered as well. E-Health is defined as the delivery of health services and information through the internet and related technologies. It has developed considerably over the past years, with most e-health interventions focussing on adults, and to a lesser extent on children. For children however the use of the computer and internet is part of their daily life. Furthermore, adolescents seem to disclose more problems in online therapies compared to face-to-face interventions. For these reasons, E-Health applications are also of great value for children. E-Health in pediatric psychology

is still lagging behind and must address numerous challenges. A first step has been made for childhood cancer survivors. The psycho-educational group intervention previously described has now been reshaped into a chat-group-intervention program and determination of effectiveness is in progress (www.opkoersonline.nl).

Many parents report their children to be vulnerable. Implications of this finding could be that all parents of children with oncological illnesses get psychoeducation about this phenomenon and are coached in setting appropriate limits to and having realistic expectations of their child. This could be done by pediatric psychologists or trained nurses. Parents who are considered to be at risk should be involved in more intensive and individualized intervention programs. Doctors are also important partners, because they can encourage parents to treat their child as normally as possible during visits to the late effects clinics. Psychosocial effects of parental beliefs of vulnerability on children surviving SCT need to be studied and brief routine assessment of both parents and children, even years post-SCT or LCH treatment, is recommended.

In conclusion, results in this thesis show that even though parents of children with cancer or children undergoing SCT as a group are resilient, pediatric psychologists are challenged to develop specific targeted interventions, based on a theoretically sound and easy to use assessment of risk and need. Doctors and nurses should be aware of parents who are at risk for heightened stress, because well-functioning parents are better able to tend to the needs of their children. Following up on parental well-being is important, not only during the active phase of treatment, but also in the long run: out of sight should not be out of mind!

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9

Dutch summary/ Nederlandse samenvatting

Als ouders te horen krijgen dat hun kind kanker heeft, hebben ze het gevoel dat hun wereld instort. Veel ouders zeggen, ook jaren na een succesvolle behandeling, dat hun leven nooit meer hetzelfde is als voor de diagnose. De rol die de kinderpsycholoog in het ziekenhuis, de pediatrisch psycholoog, genoemd, kan spelen in de begeleiding van ouders en kinderen heeft in de laatste decennia een enorme ontwikkeling doorgemaakt. Doordat de sterk verbeterde (inter)nationale behandelprotocollen hebben geleid tot een veel grotere overleving dan bijvoorbeeld in de jaren rond 1960 is het accent van het werk van de pediatrisch psycholoog meer gaan liggen op het begeleiden van gezinnen bij het omgaan met een chronische ziekte dan bij het begeleiden van kinderen en hun ouders bij een naderend overlijden. Ook is de pediatrisch psycholoog, onder invloed van de collega's in de Verenigde Staten, zich steeds meer gaan toeleggen op het doen van wetenschappelijk onderzoek. Onderzoek is onder andere gericht geweest op een nauwkeurig vastleggen van de emotionele gevolgen van kinderkanker bij ouders en kinderen, geoperationaliseerd als o.a. gezondheidsgerelateerde kwaliteit van leven, angst, onzekerheid, depressieve klachten en posttraumatische stress. De term 'stress' wordt daarbij veelal als overkoepelende term gebruikt. Gebaseerd op de theorie van Lazarus en Folkman wordt er een onderscheid gemaakt tussen stressoren, ofwel de prikkels die stress kunnen veroorzaken, de appraisal, de evaluatie van de stressor en de manifestaties van stress ofwel de stress reacties.

Dit proefschrift bevat vijf gepubliceerde artikelen en één artikel dat nog bij een tijdschrift ligt voor beoordeling, over de manier waarop vooral ouders, maar ook kinderen zelf omgaan met de levensbedreigende ziekte kanker en met een mogelijk levensreddende behandeling als een beenmergtransplantatie (BMT). Ook is er een hoofdstuk gewijd aan de niet-medische gevolgen van de zeldzame ziekte Langerhans Cell Hystiocytose (LCH) bij kinderen. Het LUMC is een expertisecentrum voor kinderen met deze ziekte.

Hoofdstuk 1 is een inleidend hoofdstuk, waarin een overzicht van de stand van zaken van het pediatrisch psychologisch onderzoek wordt gepresenteerd en waarin tevens huidige en toekomstige onderzoeksgebieden worden beschreven. Met betrekking tot de gevolgen van kanker wordt in dit hoofdstuk het model van Kazak gepresenteerd (medisch traumatisch stress model). Dit model heeft veel onderzoek gegenereerd en lijkt een goed passend model om reacties van kind en ouders op kanker te beschrijven. In dit model wordt onderscheid gemaakt tussen drie verschillende fasen bij medisch-traumatische gebeurtenissen, namelijk de peri-traumatische fase (bijvoorbeeld de periode rond diagnose), een vroege post traumatische fase (gebeurtenissen en reacties tijdens de behandeling van het kind) en een late posttraumatische fase die gevolgen op lange termijn beschrijft.

In **Hoofdstuk 2** worden de resultaten van een grote overzichts studie naar stress en aanpassing van ouders van een kind met kanker gepresenteerd. In de 57 artikelen die in dit artikel besproken worden, komt een breed scala van onderzoek aan bod waarin stress bij ouders op veel verschillende manieren geoperationaliseerd wordt. Stress blijkt het hoogst te zijn rondom de diagnose, bij het merendeel van de ouders zakt de stress tot 'normale' niveaus. Risicofactoren voor verhoogde stress (i.e. verhoogde angstscores, depressieve klachten, onzekerheid en posttraumatische stress) zijn onder andere: lager opleidingsniveau en lagere sociaal-economische status, hoge stress bij diagnose, al bestaande psychische klachten (vooral angstklachten), gedragsproblemen bij het kind en onvoldoende ervaren sociale steun.

Er zijn in het Nederlandse taalgebied tot nu toe weinig ziektegerelateerde of ziektespecifieke vragenlijsten voorhanden om emotionele gevolgen bij ouders van zieke kinderen in kaart te brengen. Men moet daardoor vrijwel altijd een toevlucht nemen tot generieke vragenlijsten, die als nadeel hebben dat ouders van zieke kinderen vergeleken worden met 'gezonde' normgroepen, wat een goede vergelijking bemoeilijkt.

Hoofdstuk 3 bevat de resultaten van een multidisciplinair onderzoek naar de psychometrische kenmerken van de Nederlandse vertaling van een Amerikaanse ziektegerelateerde vragenlijst, de Pediatric Inventory for Parents (PIP). In samenwerking met het Universitair Medisch Centrum Groningen en het Wilhelmina Kinderziekenhuis in Utrecht zijn 174 ouders van kinderen, die tussen de 2 en 18 maanden geleden gediagnosticeerd zijn met kanker, onderzocht. Ouders (zowel vaders als moeders) vulden de PIP en drie andere vragenlijsten eenmalig in. De interne consistentie, test-hertest betrouwbaarheid en validiteit van de Nederlandse vertaling van de PIP is voldoende. De PIP correleert hoog met angst (gemeten met de State Trait Anxiety Index) en met algemene stress (gemeten met de General Health Questionnaire). Het oorspronkelijke vier-factorenmodel van de Amerikaanse PIP is teruggevonden, zij het met 39 van de 42 items. Geconcludeerd werd dat de PIP, mits verder psychometrisch onderzocht, bruikbaar zou zijn in de praktijk voor het vaststellen van ziektegerelateerde stress bij ouders. Op basis van het in dit artikel beschreven onderzoek is voor het onderzoek naar lange termijn gevolgen bij ouders na de BMT van hun kind (Hoofdstuk 6) een verkorte versie van de PIP ontwikkeld en gebruikt, die daar verder wordt besproken.

Hoofdstuk 4 is een overzichtsartikel (review) van 18 artikelen die in de laatste twintig jaar zijn verschenen over stress bij ouders van kinderen die een beenmergtransplantatie hebben moeten ondergaan. Er was op dit terrein nog niet eerder een review gepubliceerd. Uit de beschreven artikelen blijkt dat stress bij ouders het hoogst is vlak vóór de opname en tijdens de acute fase van de BMT. Bij de meeste ouders zakt de stress in de 3-12 maanden na ontslag terug tot niveaus vergelijkbaar met de normgroepen (meestal ouders van gezonde kinderen of baseline niveaus van de ouders zelf voorafgaand aan BMT), maar een subgroep van ouders blijft, ook 18 maanden na de BMT van hun kind stressklachten rapporteren. Eén van de belangrijkste voorspellers voor

stress op de langere termijn is de aanpassing tijdens de acute fase van de BMT. Ouders (NB, de studies betroffen voornamelijk moeders) die de BMT als een bedreiging zagen voor hun kind, moeders die op problemen reageerden met ontkenning of herbelevingen, moeders met een onvoldoende steunende gezinsomgeving of moeders die depressieve klachten hadden ten tijde van de BMT liepen het meeste risico op langere termijn stress.

In **Hoofdstuk 5** worden de resultaten gepresenteerd van een longitudinaal onderzoek bij ouders en kinderen en adolescenten voor en gemiddeld 10 maanden na een BMT. Zowel de ouders als kinderen en jongeren vulden kwaliteit van leven vragenlijsten in en hieruit kwam naar voren dat de algehele kwaliteit van leven van deze kinderen en adolescenten onveranderd bleek, 10 maanden na de BMT, maar dat het functioneren thuis (als onderdeel van de kwaliteit van leven) slechter werd ervaren door zowel kinderen zelf als hun ouders. Ook voelden ouders zich na de BMT minder competent als opvoeders. Opvoedingsstress bij ouders, en in het bijzonder de mate waarin ouders hun kind als veeleisend beschouwden, was een voorspeller van de door ouders beoordeelde kwaliteit van leven van hun kind. Jongere kinderen rapporteerden een hogere kwaliteit van leven dan oudere kinderen. Er is nog weinig bekend over de emotionele gevolgen van een BMT bij ouders op de lange termijn.

In **Hoofdstuk 6** worden de resultaten vermeld van een cross-sectioneel onderzoek dat is gedaan bij ouders 5 en 10 jaar na de BMT van hun kind. Uit dit onderzoek blijkt dat ouders, 10 jaar na de BMT van hun kind, algemene stressscores rapporteren die vergelijkbaar zijn met de Nederlandse normgroep van dezelfde leeftijd. De gemiddelde stressscore van ouders 5 jaar na BMT is eveneens vergelijkbaar met de normgroep, maar het percentage moeders dat boven de drempelwaarde score van 2 scoort op de algemene stressvragenlijst (i.e. de General Health Questionnaire, GHQ) is significant hoger dan de normgroep (40% versus 26%). Uit het onderzoek bleek eveneens dat de ouders uit de onderzoeksgroep veel hogere scores rapporteerden op 'perceived vulnerability', ofwel de door ouders beleefde kwetsbaarheid van het kind. Zelfs 10 jaar na de BMT van hun kind ziet 74% van de ouders hun kind nog als extreem kwetsbaar. Vijf jaar na de BMT is dat percentage 96%. Vaders en moeders verschillen hierin niet van elkaar.

De ervaren kwetsbaarheid is deels te verklaren doordat veel van de kinderen na BMT ook daadwerkelijk kwetsbaar zijn, door late effecten van ziekte en behandeling, kans op terugkeer van de ziekte of een secundaire maligniteit. Ook zal traumatisering van de ouders een rol spelen in de manier waarop ze naar hun kind kijken: een groep ouders heeft nog lange tijd na de BMT last van posttraumatische stressklachten als herbelevingen, verhoogde prikkelbaarheid en de neiging pijnlijke herinneringen uit de weg te gaan. Kwetsbaarheidsbeleving bij ouders kan ertoe leiden dat ze minder grenzen stellen aan hun kind en hun kind tegelijkertijd ook minder ruimte geven om zich los te maken. Uit eerder onderzoek met prematuur geboren kinderen bleek dat kwetsbaarheidsbeleving

ertoe leidde dat kinderen minder vrij werden opgevoed, minder leerervaringen opdeden en minder zelfvertrouwen ontwikkelden.

Hoofdstuk 7 vermeldt de resultaten van een onderzoek bij kinderen met Langerhans Cell Hystiocytose (LCH), een zeldzame niet-maligne ziekte, waarbij een woekering optreedt van een bepaald type witte bloedcel, de histiocyten, in de weefsels. Daardoor komt de functie van het aangedane lichaamsdeel in het gedrang. LCH is een grillige ziekte; een patiënt kan een beperkte aantasting hebben in een enkel lichaamsdeel en niet of nauwelijks behandeling nodig hebben. Er zijn ook patiënten die een levensbedreigende multi-systeem variant hebben en behandeld moeten worden met chemotherapie. In dat laatste geval gaat het vooral om zeer jonge kinderen. In ons onderzoek is gekeken naar de gevolgen van LCH op cognitief, gedragsmatig en emotioneel gebied. Kinderen met LCH bleken aanzienlijk vaker speciaal onderwijs nodig te hebben dan de gewone populatie (25% versus 3-5%), volgens hun leerkrachten en ouders vertonen ze meer internaliserend (naar binnen gericht) probleemgedrag en deze kinderen beoordelen hun kwaliteit van leven lager dan hun gezonde leeftijdsgenoten, vooral de oudere kinderen.

In de **Discussie** worden alle hoofdstukken samengevat en de beperkingen van de zes onderzoeken besproken. Ook worden suggesties gedaan voor toekomstig onderzoek.

Beperkingen van de onderzoeken zijn vooral de lage aantallen in de onderzoeksgroepen, door de zeldzaamheid van de ziekte en behandeling met BMT, door te hoge stress bij ouders of juist het te druk hebben met andere dingen buiten de ziekte en door taalproblemen bij niet van origine Nederlandse ouders. Hierdoor worden statistische analyses en het trekken van harde conclusies bemoeilijkt. Ouders van kinderen met verschillende diagnoses (en behandeltrajecten en late effecten) worden noodgedwongen als één groep behandeld, terwijl er grote onderlinge verschillen zijn en navenante verschillen in stress bij ouders. Het is overigens in alle onderzoeken gelukt om een hoog percentage vaders in het onderzoek te betrekken, wat in veel studies tot nu toe veelal niet het geval was. Een andere beperking ligt in de overwegend traditionele manier van onderzoek doen onder psychologen en andere sociale wetenschappers, namelijk via schriftelijke zelfrapportage. Dit heeft als nadeel dat ouders die de Nederlandse taal niet machtig zijn, niet goed kunnen deelnemen aan het onderzoek. Hierdoor is de onderzoeksgroep niet representatief voor de hele populatie. Ook brengt zelfrapportage het risico van 'response style' met zich mee, ofwel het consequent over- of onderrapporteren van klachten. Traditioneel worden vooral 'algemene' vragenlijsten gebruikt om psychologische reacties van ouders in kaart te brengen. Voordeel hiervan is dat de gegevens gemakkelijk te vergelijken zijn met resultaten uit ander onderzoek. Nadelen zijn dat de specifieke problemen van ouders van ernstig zieke kinderen niet herkend worden, bovendien worden de reacties van ouders teveel als 'pathologisch'

beschouwd, terwijl het logischer is om ouders te beschouwen als 'normale' mensen in een abnormale situatie.

Vanuit de diverse onderzoeken kunnen de volgende aanbevelingen voor de toekomst worden gedaan. Allereerst bestaat er een behoefte aan goede instrumenten en onderzoeksprocedures die stress en adaptatie in kaart kunnen brengen bij ouders van ernstig zieke kinderen. Kwalitatieve studies, bijvoorbeeld door middel van interviews, kunnen een belangrijke aanvulling vormen op traditionele vragenlijsten, zeker als de beleving van niet-Nederlandse ouders in kaart gebracht moet worden. De timing van de metingen is ook van belang, want het maakt veel uit of een ouder enkele dagen of weken na de diagnose van zijn of haar kind wordt ondervraagd, of als de behandeling is afgerond. Consensus over de 'ideale' momenten in de behandeling van een kind met kanker waarop ouders bevraagd moeten worden zou kunnen helpen bij het meer uniform maken van onderzoeksresultaten en bij het verbeteren van de zorg voor deze ouders. Metingen op bijvoorbeeld een maand na diagnose, 6 en 12 maanden na diagnose (de fase van de actieve behandeling) en bij het einde van de behandeling zouden kunnen bijdragen aan zowel het onderzoek als de klinische praktijk. Lange termijn follow up blijft noodzakelijk om die ouders te identificeren die klachten blijven houden. Het zou de pediatrische psychologen in Nederland erg helpen als er een betrouwbaar en gemakkelijk te gebruiken screeningsinstrument beschikbaar zou zijn, waarmee ouders die extra begeleiding nodig hebben op een snelle manier geïdentificeerd kunnen worden. Ook moeten psychologen manieren ontwikkelen om de kosten en opbrengsten van hun interventies te meten, zodat nog duidelijker wordt welke rol de psychologie in het ziekenhuis speelt.

Zodra duidelijk is welke ouders behoefte hebben aan intensievere begeleiding, zullen korte, praktische en gemakkelijk te gebruiken interventies ingezet moeten worden. Psychoeducatie zal voor veel ouders een belangrijk onderdeel zijn van de interventies. Zo is er recent een DVD gemaakt voor ouders van kinderen die een beenmergtransplantatie moeten ondergaan, waarin allerlei praktische zaken rond de fases voor, tijdens en na de BMT besproken worden door vier ouderparen die het traject al achter de rug hebben. Tijdens de opname van het kind krijgen de meeste ouders voldoende steun van hun eigen netwerk, de professionals in het ziekenhuis en van andere ouders. De grootste uitdaging voor ouders van kinderen die een BMT ondergaan vormt de periode na ontslag, waarin de zorg volledig op ouders neerkomt. Dat is vaak ook de periode waarin de sociale steun afneemt, omdat de omgeving verwacht dat het ergste nu wel achter de rug zal zijn. Hetzelfde is te zien bij ouders van kinderen met kanker na het einde van de behandeling. Het is belangrijk dat ouders juist in deze fase de ondersteuning krijgen die ze nodig hebben.

Kwetsbaarheidsbeleving bij ouders van kinderen met een levensbedreigende ziekte is een punt van zorg, zeker op de langere termijn. Voor veel ouders kan het al helpen als er voorlichting over dit onderwerp wordt gegeven, zodat ze alert kunnen zijn op hun eigen percepties en gedrag. Ook zouden ouders –individueel of in groepsverband, door een psycholoog of getrainde verpleegkundige- gecoacht kunnen worden in het weer 'gezond gaan opvoeden' van kinderen na behandeling van een ernstige levensbedreigende ziekte.

Curriculum Vitae
List of abbreviations

Curriculum Vitae

Jantien Wiersma werd geboren op 8 juni 1969 in Den Haag als kind van Marijke van Soest en Enno Wiersma, haar zusje Heleen en broertje Klaas werden respectievelijk in 1971 en 1974 geboren. Ze doorliep met veel plezier Montessorischool Waalsdorp en vervolgens het Eerste Vrijzinnig Christelijk Lyceum in Den Haag, waar ze in 1987 haar gymnasiumdiploma behaalde.

Na een jaar gestudeerd te hebben aan een Amerikaanse universiteit (Luther College, Iowa) begon Jantien in 1988 met haar studie Psychologie in Groningen, aangevuld met een semester aan een andere Amerikaanse universiteit (Frostburg University, Maryland). Haar stage liep zij bij de Schoolbegeleidingsdienst Groningen. In begin 1994 studeerde zij af met als hoofdrichting Ontwikkelingspsychologie en nevenrichtingen Klinische- en onderwijspsychologie.

Na een werkervaringsplaats van een jaar in het toenmalige Pedologisch Instituut Duivendrecht kwam zij in 1995 terecht bij de Schoolbegeleidingsdienst Amstelland en de Meerlanden in Hoofddorp. Hier leerde zij goed en snel basisschoolleerlingen te diagnosticeren, met schoolteams en individuele leerkrachten te werken en cursussen te ontwikkelen en te geven. Jantien bekwaamde zich onder andere ook in de Video Interactiebegeleiding en in gedragstherapie bij kinderen en adolescenten. In deze periode begon Jantien tevens met haar eigen praktijk aan huis voor advies en begeleiding gericht op ouders, kinderen en adolescenten. Deze praktijk is later Vrijmoet & Maatman geworden.

Ze trouwde in 2000 met Daan Vrijmoet. In 2001 werd haar zoon Wouter geboren en in 2002 kwam Kees.

Na zeven jaar, in november 2002, veranderde Jantien van baan en werd zij gz-psycholoog op de afdeling Kindergeneeskunde van het LUMC. Aanvankelijk hield de baan uitsluitend patiëntenzorg in, maar na een aantal jaren (in 2005) won de nieuwsgierigheid het van de twijfel en begon Jantien data te verzamelen over stress en coping bij ouders van kinderen die een beenmergtransplantatie moesten ondergaan.

Van het één kwam het ander...

List of abbreviations

ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
BMT	Bone Marrow Transplantation
CBCL	Child Behaviour Check List
CFA	Confirmatory factor analysis
CNS	Central Nervous System
CVS	Child Vulnerability Scale
DI	Diabetes Insipidus
DUX	Dutch Children's AZL/TNO Quality of Life Questionnaire
GHQ	General Health Questionnaire
HRQoL	Health Related Quality of Life
IQ	Intelligence Quotient
JMML	Juvenile Myelomonocytic Leukemia
LCH	Langerhans Cell Histiocytosis
MANOVA	Multivariate Analysis of Variance
MDS	Myelodyplastic Syndrome
p	probability
PIP	Pediatric Inventory for Parents
PSI	Parental Stress Index
PTSS	Posttraumatic Stress Symptoms
RMSEA	Root Mean Square Error of Approximation
SAA	Severe Aplastic Anemia
SCID	Severe Combined Immune Deficiency syndrome
SCT	Stem Cell Transplantation
SF	Short Form
SPSS	Statistical Package for the Social Sciences
SRMR	Standardized Root Mean Square Residual
STAI	State Trait Anxiety Index
TLI	Tucker-Lewis index
TRF	Teacher Report Form
WISC III	Wechsler Intelligence Scale for Children- Third Edition
WLSMV	Weighted Least Squares Means and Variance Adjusted Estimation
yrs	years
YSR	Youth Self Report