Care for consequences in children treated for leukemia or brain tumor
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Summary in English

In the Netherlands approximately 600 children are diagnosed with cancer each year, of which approximately 110 are diagnosed with a brain tumor and 140 are diagnosed with leukemia. The overall survival rate of children treated for cancer has increased substantially as a result of ever-improving treatment strategies. Unfortunately, the increase in childhood cancer survival rates has not come without a “cost”. As a consequence of the tumor and its treatment, childhood brain tumor survivors (CBTS) and survivors of acute lymphoblastic leukemia (ALL) are at considerable risk for a variety of physical, neurocognitive and/or psychosocial problems. These problems are considered as ‘late effects’ from the cancer and its treatment. These late effects have a negative impact on daily life and emphasize the need for (systematic) aftercare.

Based on literature and clinical experience, CBTS who were treated with surgery and adjuvant therapy including chemotherapy or radiation therapy or a combination seem to be at greatest risk for late effects. Recent research shows that these late effects also occur in survivors treated with surgery only.

Chapter 1 is the general introduction of this thesis, describing the medical aspects of brain tumors and ALL, their treatment and long-term consequences of brain tumors and leukemia and their treatment, and what is needed for survivors at risk for long-term consequences. Main findings of previous studies on late effects are summarized. Childhood brain tumors can roughly be categorized into low-grade tumors and high-grade tumors which are fast-growing and aggressive. Low-grade brain tumors are more often treated with neurosurgery only, while high-grade brain tumors are mostly treated with neurosurgery and adjuvant therapy; cranial radiation therapy (CRT) and/or chemotherapy.

As a consequence of the tumor and its treatment, CBTS run the risk for late effects: physical, neurocognitive, and psychosocial problems. Physical late effects are described as loss of energy and fatigue, neurological, neurosensory impairments and endocrine side effects, body changes (such as scars, hair loss or short posture) and risk for a secondary malignancy. CBTS, especially those treated with CRT, and ALL survivors treated with CRT until 1990 are at risk for neurocognitive late effects. Neurocognitive late effects often present with a decline in learning capacities based on problems with underlying basic cognitive skills such as information processing speed, attention and working memory. These problems, although more subtle, have also been described in CBTS treated with surgery only, and ALL survivors treated with chemotherapy.
The neurocognitive late effects seem to be related to white matter damage in the brain. Next to these physical and neurocognitive late effects, psychological and social late effects have been described. Also, symptoms of overall distress and impaired quality of life have been found.

As late effects can have a substantial impact on the child's development, they should be detected in time in order to refer patients to specialized aftercare. The need for aftercare for CBTS treated with adjuvant therapy seems obvious, but the recognition of the need for aftercare in CBTS treated with surgery only is less obvious and it is not known whether their needs for aftercare are identified in time. Besides adequate identification of late effects, the importance of effective interventions is high, due to the influence of particular reduced neurocognitive functioning on the overall development of the child. To date, only a few intervention programs have been developed and investigated.

Therefore this thesis includes explorative studies of the scope of late effects for CBTS and ALL survivors, years after treatment. The aim of this thesis was to describe these late effects and need for aftercare from parents' and children's perspective. Subsequently we aimed to study whether white matter damage in the brain can be related to a decline in speed of processing and motor speed in young childhood cancer survivors. And finally, two interventions are examined in survivors aimed at reducing the neurocognitive late effects. Participants in this study were at a median of approximately 6 years after the end of treatment.

In Chapter 2, parents' perspective on the existence of late effects and the detection of the need for aftercare for these late effects was evaluated in 42 CBTS. Results demonstrated that the majority of the CBTS experience several forms of late effects: physical (90%), neurocognitive (74%), emotional (64%), and social (57%). Parents reported that these late effects required aftercare. Furthermore one-third of the parents reported parenting problems and a need for aftercare, but this need was not always met. No differences in need for aftercare were found between CBTS treated with (n=22) and without adjuvant therapy (n=20). Most survivors received aftercare although a substantial delay and self-referral were frequently reported. Furthermore, parents showed a lack of knowledge about and use of aftercare services. We conclude that although professional aftercare providers respond appropriately to physical health problems, increased awareness and a more timely response is needed for neurocognitive, psychosocial and parenting problems.

In Chapter 3, Health Related Quality of Life (HRQOL) of 34 CBTS was evaluated using the KIDSCREEN-52 and compared to the norm population. Although HRQOL in most domains appeared similar to the norm population, their HRQOL scores
were significantly lower in the domains of “physical well-being and psychosocial well-being” and “peers and social support”. The risk for impaired HRQOL (T-score ≥1 SD below the norm population mean) in the domains of “physical well-being”, “moods and emotions”, “peers and social support” and “bullying” was 35 to 53% compared with 16% in the norm group. No differences between CBTS treated with (n=17) and without adjuvant therapy (n=17) were found. Although HRQOL in most domains appeared similar to the norm population, a considerable number of CBTS reported impaired HRQOL on physical well-being, and psychological and social functioning. We recommend to systematically monitor HRQOL in all CBTS, regardless of the therapy applied.

Chapter 4 describes the relation between white matter fractional anisotropy (WMFA) visualized with Diffusion Tensor Imaging (DTI) on a 3.0-T MRI, and cognitive functioning in 6 CBTS and 11 leukemia survivors. Significant mean WMFA and lower WMFA in parts of the corpus callosum and right inferior fronto-occipital fasciculus were found in the patient group compared to the age-matched control group (n=17). Lower WMFA was found in medulloblastoma survivors, but also in ALL survivors treated with high doses of methotrexate (MTX) compared to the control group. Significant positive correlations were present between processing speed test scores and motor speed and WMFA in parts of the corpus callosum and right inferior fronto-occipital fasciculus. We conclude that DTI on a 3.0-T MRI is sensitive for the detection of changes in white matter integrity and correlates with slow processing speed.

In Chapter 5 the feasibility of neurofeedback training (NFT) as a neurocognitive intervention for CBTS with neurocognitive late effects was evaluated in 9 CBTS. NFT is based on operant conditioning in which self-regulation of brain activity depicted by EEG is taught. The training consisted of 30 sessions NFT and was evaluated as being enjoyable and recommendable for other survivors. Based on the neuropsychological pre- and post test scores, we found indications for improved information processing speed. These improvements were also mentioned by participants after the training. This pilot study indicates that NFT is a feasible intervention for CBTS with neurocognitive late effects. Further research is necessary to study the effectiveness of NFT in CBTS.

In Chapter 6 the effect of growth-hormone (GH) therapy during a period of 24 months on neurocognitive functioning in 20 ALL survivors, most of whom were treated with CRT, was evaluated. Survivors with reduced bone mineral density (≤1 SD) and/or low IGF-I SD-scores (≤1 SD) were included in the study. At baseline assessment participants scored average on cognitive tests, in contrast of our expectations. We found that GH treatment has positive effects on visual-spatial long-term memory.
and attention, but is also seems to have a negative effect on verbal memory functions. The findings from this study indicate that more information on cognitive effects of GH treatment is warranted before GH treatment may be recommended to enhance cognitive functions in ALL survivors.

In the general discussion (Chapter 7), the main findings of the studies are considered and clinical implications and recommendations for further research are described.

**Seven take home messages are formulated:**

1. Late effects are commonly experienced by CBTS;
2. There is a considerable need for aftercare for the late effects, but this need is not always identified on time;
3. Special attention is required for survivors who were treated with surgery only in order to prevent underestimation of their late effects;
4. More than one-third of the CBTS are at risk for impaired HRQOL for physical well-being, psychological and social functioning;
5. White matter tracts show impairment in pediatric cancer survivors and correlate with the slow information processing speed in CBTS;
6. Neurofeedback training is a feasible intervention for CBTS who suffer from neurocognitive late effects;

Subsequently, limitations of the studies are considered, which include the small sample size, the single center studies and the representativeness of our study groups, the explorative nature of the studies, and some non-standardized questionnaires. Based on these limitations, several recommendations for future research are suggested. Regarding the high prevalence of late effects, it is recommended to design longitudinal research and to explore the impact and interaction of late effects in daily life. In addition, it is needed to better understand how white matter damage develops during treatment using imaging techniques.

Regarding the unmet needs during aftercare, it is recommended to develop effective screening tools. In addition it is recommended to develop and evaluate interventions that reduce cognitive problems and to improve coping with late effects. Collaboration between treatment centers and financial resources are necessary to improve aftercare.

Furthermore, this thesis describes implications of this study for clinical practice. The importance of routine multidisciplinary aftercare for all CBTS, regardless of the therapy applied, is suggested. The aftercare should focus on regularly and systematic
informing, monitoring and screening late effects. Detecting the need for aftercare in time enables to timely provide appropriate aftercare services and neurocognitive and psychosocial interventions. The hospital school teacher or school liaison could bridge the gap in knowledge between the hospital and school and should play an important role with regard to all the different aspects of aftercare. In addition, the survivors’ school should play an important role in early signalizing late effects and should be involved in providing aftercare. ICT techniques such as specifically designed websites and smartphone applications could be helpful in providing information about late effects. In addition, ICT techniques could also be helpful in monitoring (neuro) psychological functioning.

Finally, this thesis demonstrates that long-term brain tumor survivors suffer from several late effects of their disease and their treatment many years after having been cured. Not only survivors who were treated with surgery and adjuvant therapy, but also survivors who were treated with surgery only can experience several late effects. Systematic aftercare is needed to monitor (neuro) psychological functioning and needs, to screen and identify survivors at risk and to be able to provide adequate aftercare in time.