Illness representation and cognitive functioning among pediatric cancer patients

PhD thesis

Annamária Szentes

Semmelweis University
Doctoral School of Mental Health Sciences

Supervisors: Dr. Ferenc Túry, PhD
Dr. Szabolcs Török, PhD

Official reviewers: Dr. Gergely Kriván, PhD
Dr. Gábor Csukly, PhD

Head of the Final Examination Committee: Dr. László, Tringer, PhD
Members of the Final Examination Committee: Dr. Dóra Perczel-Forintos, PhD
Dr. Eszter Biró, PhD

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INTRODUCTION

As a result of medical advances over the past 30 years, the survival rate of paediatric cancer patients has increased dramatically (Ward et al, 2014). Since then, the behavioural and psychosocial functioning of paediatric cancer patients has been widely documented (Patenaude & Last, 2001). Research results have indicated that the psychosocial and neurocognitive consequences of cancer and its treatment can have adverse lifelong effects and that psychosocial support is critical when caring for children with cancer (Wiener et al, 2015). Surprisingly, according to some research, children with cancer are emotionally well-adapted compared to normal children or children living with other medical conditions (Leisenring et al., 2009). Although many childhood cancer patients cope effectively during the course of their illness (Phipps et al, 2005) and demonstrate resilience in long-term adjustment and quality of life (Kazak et al., 2012; Zebrack & Chesler, 2002), some studies have identified areas that are problematic for paediatric cancer survivors. These are, for example, social relationships (Zeltzer et al., 2009), academic achievement (Palmer et al., 2013), self-concept and self-esteem (Moore et al, 2009). These authors reasoned that cancer patients have to face multiple stressors, including serious medical side effects, significant changes in their daily lives and disruption of social and family life (Werba & Kazak, 2008). They also undergo painful procedures, hospitalisation and uncertain prognoses, all of which are common stressors that could pose a substantial threat to their adjustment (Kazak et al, 2009). Consequently, the children's emotional adjustment to cancer diagnosis and treatment is determined by various factors (Firoozi & Rahmat, 2013), namely age at diagnosis, type of treatment, social and family background and the coping strategies used by children and their family. In addition to individual coping behaviour, it is essential to examine the way in which patients subjectively perceive and explain their illness and its circumstances (Fan, Eiser, Ho, & Lin, 2013). The self-regulation model, which was proposed by Leventhal et al. (2001), provides an overall framework that integrates social and contextual factors with the individual's emotions and thoughts. In the model, patients construct their own perceptions or models that help them make sense of their illness experiences, providing a basis for their own responses. However, the relationship between illness perceptions and disease outcomes has mainly been investigated among different chronic diseases, such as diabetes mellitus, asthma and chronic fatigue syndrome (Timmers et al., 2008); there are few studies (Fonseca et al., 2010) that have examined these perceptions in the paediatric cancer population. Examining illness-related perceptions among children with cancer, Hagger and Orbell (2003) highlighted that beliefs about cancer experiences are more potent predictors of posttraumatic stress disorder (PTSD) than demographic or disease and

treatment factors. Similarly, Salewski (2003) also emphasised the importance of paediatric cancer patients' illness perceptions in determining their subjective well-being, self-management and adherence to medical regiments.

As survival among children treated for cancer continues to improve, more attention is being paid to the late effects of cancer treatment. (Margelisch et al., 2015). Children who received treatment targeting the central nervous system are at greater risk for developing neurocognitive late effects than other survivors of childhood cancer (Hocking et al., 2015, Conklin et al., 2015). In children treated for brain tumours, chronic neurocognitive effects are especially challenging and have been widely studied. Besides the deterioration of overall intellect, studies have revealed that specific cognitive abilities, including attention, working memory, processing speed, psychomotor speed and visual-motor control, have shown particular vulnerability to treatment effects in medulloblastoma (MB) survivors (Conklin et al., 2015, Margelisch et al., 2015). Evidence indicates that younger age at treatment, longer time period from diagnosis, female gender, treatment intensity, mother's educational level, and chemotherapy increased the risk for low cognitive functioning after treatment (Dennis et al., 1996, Hoppe-Hirsch et al., 1990). Technical advances in radiotherapy hold promise for lowering the frequency of neurocognitive sequelae. These long-term cognitive side effects have a serious impact on children's every-day life and makes it difficult for them to reintegrate into normal social life.

Based on these data we carried out a research on the illness representations of paediatric cancer patients and on the cognitive functioning of children treated for medulloblastoma.

OBJECTIVES

In the first part of the present thesis, in a cross-sectional study design, I compared the illness representations of children with cancer and their parents to those of children with diabetes mellitus (type-1) and children with juvenile idiopathic arthritis (JIA).

In this study I have the following hypotheses:

- I hypothesise that differences will be found in the dimensions of illness perceptions among the three illness groups
- Illness specific representations can be identified among pediatric cancer patients.
- I hypothesise that parents will have more negative illness perceptions than their children.

In the second part of the present thesis, in a cross-sectional study, I examined the cognitive functioning in a homogeneous sample of Hungarian children treated for medulloblastoma.

In this study I have the following hypotheses:

- Paediatric medulloblastoma survivors show decline in global cognitive functioning compared to population norms.
- In the cognitive functioning the verbal areas are less affected than the nonverbal areas.
- Between the IQ subscales the most affected index is the Processing Speed Index (PSI).
- The most important predictive factors of cognitive impairment are the younger age at treatment, female gender, the high radiation dose, and low level education of the mother.

METHODS

1. Differences in illness perception between children with cancer and other chronic diseases and the illness perception of their parents

Sample

The participants of this study were children diagnosed with an oncological illness, diabetes mellitus (type 1) or JIA and their parents. The selection criteria for children with an oncological illness were the diagnosis of a paediatric malignant tumour or leukaemia, and that they completed active treatment within 5years. Children with cancer underwent a combination of surgery, chemotherapy and radiation therapy. Children with JIA received non-steroid anti-inflammatory drugs (NSAIDs) according to their stage of their disease. According to the protocols, children with diabetes received insulin therapy and diet to maintain normal blood sugar level. All the children were referred to the camp via Hungarian hospitals from all over the country, and every child who took part in the camp received the questionnaires. All the children who took part in the research were between the ages of 8 and 18. A total number of 184 chronically ill children and 184 caregivers (by disease groups: oncology group, n = 65; diabetes group, n = 76; JIA group, n = 43) completed the Revised Illness Perception Questionnaire (IPQ-R; Moss-Morris et al., 2002) and its proxy version.

Measuring instruments

The IPQ-R (Moss-Morris et al., 2002) was used to measure the dimensions of children's and mothers' illness perceptions. This revised version, which incorporates recent theoretical and empirical findings among paediatric chronic illnesses (Chang & Yeh, 2005), has demonstrated good reliability across several illness groups and includes eight cognitive dimensions (Moss-Morris et al., 2002; Broadbent et al., 2011). We used the official Hungarian version of the IPQ-R test translated by Reinhardt (2007).

The questionnaire has 44 items on a 5-point scale ranging from (1) 'strongly disagree' to (5) 'strongly agree'. The IPQ-R has three parts. The first part measures 'illness identity' by assessing the frequency and the number of symptoms. The illness identity dimensions measure the number of commonly experienced symptoms (e.g. upset stomach, nausea, pain, etc.) that the patient associates with his or her illness. The patient also must describe the symptoms related to the illness. Questions concerning symptoms related to the illness represent illness knowledge instead of illness identity because those who had not experienced symptoms also answered yes or no to these questions. In the second part of the questionnaire, the 'consequences' subscale measures the patient's beliefs regarding the seriousness of his or her condition. The 'timeline' dimension assesses whether a patient sees his or her illness as 'cyclical' in nature or 'acute' versus 'chronic'. The control dimension is divided into 'personal control' and 'treatment control', which refers to the belief that the treatment is an effective way of controlling the illness. The 'illness coherence' subscale measures the degree to which a patient feels he or she has a coherent understanding or model??? of his or her condition. 'Emotional representation' assesses affective responses (anger, fear, depression, etc.) to the illness. In the third part of the questionnaire, participants had to select the possible causes (e.g. chance or bad luck, altered immunity, stress or worry, etc.).

Statistical analysis

Statistical analysis was conducted using SPSS 15.0. The significance level was set to $p < .05$. Data were checked for assumption of normality (Kolmogorov–Smirnov) before the analysis. For reliability, Cronbach's alphas were calculated as indexes of internal consistency. Chi-square tests were used to detect any differences of frequencies among the groups, and three-way (disease group, gender and age group) multivariate analysis of variance was used to reveal any differences in the means of the subscales of IPQ-R for children and parents. The main aim of this analysis was to examine the differences among the disease groups. For differences between children's and parents' evaluation of illness perceptions, a 2 (source: children or parents)´ 3 (disease group)´ 2 (gender)´ 2 (age group) repeated measure analysis of variance was

used. Only two-way interactions were interpreted because of the small cell numbers. For determining the level of agreement between parent proxy reports and child self-reports, we used the intraclass correlation coefficient (ICC) for absolute agreement (interpreted using thresholds for moderate and good agreement at 0.4 and 0.6 [Bartko, 1966]).

2. Neurocognitive deficits among children with medulloblastoma

Sample

Children (n = 34) between the ages of 6 and 16 who were previously treated for MB and alive at the time of the study were selected from the 2nd Department of Pediatrics, Semmelweis University, Budapest and were offered participation in the study. The average age at measurement was 11.15 years (SD = 3.05, range, 6–16), time since diagnosis was 2.71 years (SD =1.80, range, 1.67-8) and at diagnosis was 7.53 (SD = 3.3, range, 3–15).

Treatment was carried out according to the Hungarian MBL2004/2008 schedule: maximal surgical resection, conventional chemotherapy, ithec MTX, craniospinal (for low risk patients: 28-32 Gy and for high risk patients: 33-36 Gy) and booster (18-24 Gy) radiotherapy with concomitant chemotherapy, and high dose chemotherapy with stem cell rescue (ABMT) for high-risk patients. The number of MB patients who received ABMT with high dose irradiation (33-36 Gy) was 7. The number of those who got ABMT with low dose irradiation (28-32 Gy) was 6. 12 patients received high dose irradiation without ABMT and 9 patients received low dose irradiation without ABMT. Thirty percent of mothers had primary education, 32% of them had high school education and 38% had a university degree.

Measuring instruments

The children were administered the age-appropriate Hungarian version of the Wechsler Intelligence Scale for Children - Fourth Edition (WISC–IV) (Prifitera et al, 2008). Besides the total test IQ (TTIQ), the WISC-IV has 4 scales: Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI) and Processing Speed Index (PSI) (Mlinkó, 2012).

Statistical analysis

Statistical analysis was conducted using SPSS 24.0. The significance level was set to $p < .05$. Full Scale IQ (FSIQ) scores and subscale scores were compared with one-sample t-tests to the population mean (IQ = 100) established in the validation studies of WISC (Watkins et al., 2006). Overall effect of the IQ subscale was tested with an one-way repeated measures ANOVA. Post-hoc analyses on all subscale contrasts were performed with mixed effects linear model using the lmer function from the lmerTest packages, with the WISC-IV subscale as a

predictor and a subject ID as a random intercept. We calculated the predictive interval for predicting future observations in FSIQ and subscale scores within the MB survivor population, and based on this we report the percentage of observations predicted to fall below 100 with a 95% tolerance. The effect of sex, age at treatment, time since treatment, mother education level, CSI radiation dose (dose below or equal to 32 Gy was considered low, and above 32 Gy was considered high dose), and ABMT on IQ were determined using a linear regression model containing these moderators as predictors.

RESULTS

1. Differences in illness perception between children with cancer and other chronic diseases and their parents

Children's self reports

According to the three-way (disease group, gender and age group) multivariate analysis of variance, the disease group of the children had a significant effect on the IPQ-R subscales ($F(16, 332)=12.241$, $p<.001$, partial $eta^2=.371$), while gender and age group had no effect ($F(16, 332) = 1.842$, $p > .05$, partial $eta^2 = .082$; $F(16, 332) = 1.579$, partial $eta^2 = .071$). Tests of Between-Subject Effect indicated significant differences for self-reports among the illness groups for five subscales: timeline (acute/chronic; $F(2, 172) = 50.862$, $p < .001$), timeline cyclical ($F(2, 172) = 4.001$, $p<.05$), personal control ($F(2, 172)=20.500$, $p<.001$), treatment control ($F(2, 172)=18.731$, $p<.001$) and illness coherence ($F(2, 172)=0.255$, $p<.001$). Post hoc tests revealed that on the timeline (acute/chronic) and personal control scales, the means of the diabetes group were higher than means of the JIA and oncology groups. For the timeline cyclical scale, the JIA group had higher scores compared to the diabetes group, and on the illness coherence scale, the JIA group differed significantly from the oncology and the diabetes groups; here, the JIA group had lower score. The oncology group evaluated treatment control as higher compared to the JIA and the diabetes group.

Parents' reports

Analysis of the parents' IPQ-R scores also identified a significant effect for disease group ($F(16, 332) = 16.089$, $p < .001$, partial $eta^2 = .437$), and similar to the previous analysis, gender and age did not affect parents' report of illness representation ($F(16, 332) = 0.839$, $p > .05$,

partial eta^2 = .039; F(16, 332) = 1.198, p > .05, partial eta^2 = .055). The Between-Subject Effect indicated significant differences for seven subscales of the IPQ-R: timeline (acute/chronic) (F(2, 172) = 48.081, p < .001), timeline cyclical (F(2, 172)=9.314, p<.001), consequences (F(2, 172)=3.574, p<.05), children personal control (F(2, 172) = 38.847, p < .001), treatment control (F(2, 172) = 16.479, p < .001), illness coherence (F(2, 172)=14.526, p<.001) and emotional representation (F(2, 172)=3.583, p < .05). Post hoc tests revealed that on the timeline (acute/chronic) scale, the three groups differed from each other: the parents of the diabetes group had the highest score, the parents of the oncology group had the lowest, and the score of the parents of the JIA group was in the middle. Personal control, treatment control and illness coherence scores for the diabetes group differed from the other two groups significantly: these parents evaluated their children's personal control and illness coherence as higher, while treatment control score was lower compared to the parents of the other two groups. On the emotional representation scale, the parents of the diabetes group showed lower scores than the parents of the JIA group. The parents of the oncology group evaluated consequences with higher scores than the parents of the JIA and the diabetes groups, while the parents of the JIA group had higher scores on the timeline cyclical scale than the parents of the other two groups.

Parent–child agreement and differences in illness perceptions

Agreement between children and their parents on illness perceptions ranged from ICC = .25 to .68, reflecting low, moderate and good agreement between children and their parents. Discordance between parents' report and children's self-report was the greatest for beliefs regarding illness variability and unpredictability (timeline cyclical scale). Children and their parents were most likely to agree on the number of symptoms and on the nature of the illness (acute or chronic). For the controllability (personal control and treatment control) and for the consequences of the illness, there was moderate agreement between children and their parents.

To examine any differences in illness representation between children and their parents, a 2 (source: children or parents)′ 3 (disease group)′ 2 (gender)′ 2 (age group) repeated measure analysis of variance was computed. When multivariate analysis indicated significant results, the source of these effects was identified through univariate analysis. There was a significant effect for source, that is, children or parents as a Within-Subject Effect (F(8, 165)=36.554, p<.001, partial eta^2=.639), while for source and disease group (F(16, 332) = 1.639, p < .1), we found only a tendency to have significant contributions to the IPQ-R subscales. Univariate analysis indicated that there were dissimilarities between children's and parents' evaluation of

illness representation on timeline (acute/chronic; $F(1, 172) = 24.272$, $p < .001$), timeline cyclical ($F(1, 172)=13.525$, $p<.001$), consequences ($F(1, 172)=51.638$, $p<.001$), illness coherence ($F(1, 172) = 5.995$, $p < .05$) and emotional representation ($F(1, 172) = 251.639$, $p < .001$). Except for illness coherence, for the other four scales, parents had higher scores than their children. For personal control ($F(2, 172)=3.155$, $p<.05$) and for illness coherence ($F(2, 172)=5.300$, $p<.01$) a significant interaction between source and disease group was identified. For both scales, the parents of the oncology group evaluated the representation differently showing lower scores. For symptoms, a significant source and gender interaction was revealed ($F(1, 172) = 4.536$, $p < .05$). Parents of girls reported more symptoms ($M = 7.47$, $SD = 3.25$ and 95% CI=[6.83, 8.11]) than their children ($M=6.89$, $SD=3.74$ and 95% CI=[6.06, 7.54]), while parents of boys ($M = 7.38$, $SD = 3.76$ and 95% CI = [6.58, 8.18]) evaluated symptoms slightly lower than their children ($M = 7.79$, $SD = 3.65$ and 95% CI = [7.01, 8.57]).

2. Neurocognitive deficits among children with medulloblastoma

Declines in global IQ and in specific IQ domains

The FSIQ and the WISC subscale indices of the MB patients were significantly lower than the population mean (FSIQ: t(33) = -4.12, p < .001, mean = 86.41 [95% CI 79.70–93.13]; Verbal Comprehension Index (VCI): t(33) = -2.26, p = .031, mean = 93.21 [87.09–99.32]; Perceptual Reasoning Index (PRI): t(33) = -3.78, p < .001, mean = 87.76 [81.14–94.33]; Working Memory Index (WMI): t(33) = -4.09, p < .001, mean = 88.21 [82.3394.08]; Processing Speed Index (PSI): t(33) = -5.01, p < .001, mean = 84.15 [77.71–90.58]).

There was significant difference between the scores of the different WISC subscale indexes (F[3, 99] = 4.05, p = .009). Post-hoc analyses revealed that this is due to the VCI scores being significantly higher than PRI and PSI scores, but not WMI scores (VCI vs. PRI: t = -2.09, p = .039, mean difference = -5.47 [-10.6–-0.34]; VCI vs. WMI: t = -1.91, p = .059, mean difference = -5 [-10.13–0.13]; VCI vs. PSI: t = -3.46, p < .001, mean difference = -9.06 [-14.19–-3.93]). Differences in other contrasts were not significant (ts < 1.99, ps > .059).

Effects of predictors on global IQ

The linear regression model containing sex, age at treatment, time since diagnosis, mother's educational level, radiation dose, and ABMT as predictors was a significant predictor of FSIQ (Adj. R^2 = 0,36, F[6, 27] = 4,03, p = 0,005). Of the six predictors, high radiation dose (β = -

0,38, p = 0,017), ABMT (β = -0,37, p = 0,023), and the moher's educational level (β = 0,32, p = 0,038) were significant risk factors for lower IQ while age at diagnosis (β = -0,12, p = 0,474), sex (female: β = 0,209, p = 0,213), and time period from diagnosis (β = -0,20, p = 0,207) were not significant predictors. ABMT and high irradiation dose had an impact on global IQ on their on rights.

Effects of predictors on IQ subscales

We also used the linear regression model containing sex, age at treatment, time since diagnosis, mother's educational level, radiation dose, and ABMT for predicting the effect of risk factors on IQ subscales. We found that treatment characteristics (radiation dose and ABMT) and the mother's educational level were the most important predictors for decline in specific IQ subscales.

DISCUSSION

In the *comparative assessment of illness representations* we found that the illness representations of chronically ill children were different from one another. We could identify illness representations that are specific for the given oncologic patient group. When comparing the three groups of patients, we have found that children with cancer were different on the treatment control dimension from diabetic children and from children with JIA. Children with cancer felt they had greater control over the treatment than children in the other two patient groups. We have also found that the illness representations of parents of children with cancer are more negative than those of the patients themselves. Compared to their parents, children with cancer perceive their illness more coherently. In addition, parents of this patient group deemed the illness of the children less controllable compared to their children.

When examining the cognitive functioning of children with brain tumor, we were the first to perform a comprehensive assessment of the neurocognitive functioning of children treated for medulloblastoma in Hungary. Our results highlight that child survivors of MB suffer from long-term cognitive impairment, which underlines the need for early preventive, corrective or therapeutic intervention. In addition to the decline in global functioning in IQ, children with brain tumor showed different levels of impairment in specific IQ domains as a result of treatment. Some specific IQ subscales (processing speed, working memory, perceptual reasoning) show special vulnerability of MB patients. As far as the intelligence profile is concerned, we have found that the nonverbal functions are more affected than the verbal areas

in terms of impairment. We have also found that the processing function was the most affected. We have identified the effect of radiation dose, transplantation, furthermore, the low level of education of the mother as potential risk factors concerning late cognitive deficit.

CONCLUSIONS

Based on the results of the present study, my conclusions are as follows:

1. We found that in the Hungarian sample of pediatric cancer patients and children with diabetes and children with juvenile idiopathic arthritis have different illness representations.

They beleived in the efficacy of the treatment to cure or manage the illness the most.

1. Children with cancer differed from children with diabetes and children with juvenile idiopathic arthritis in the control treatment dimension. This means that children with cancer believed in the effectiveness of their treatment the most, and this dimension seemed to be a childhood cancer-specific illness perception dimension.
2. Comparing the illness representations of children and those of their parents, we found that these differ. Parents had more pessimistic attitudes towards the illness of their child (having more consequences and feel more chronic) than their children.
3. Our study of the Hungarian paediatric medulloblastoma population confirmed the development of long term neurocognitive side effects.
4. In contrast to their healthy peers, children who have been treated for medulloblastoma exhibit significant decline in global IQ.
5. As far as the intelligence profile is concerned the nonverbal functions are more affected than the verbal areas. The most affected subscale was the Processing Speed Index (PSI), while the less affected subscale was the Verbal Comprehension Index (VCI).
6. We have also identified the most significant risk factors that had an impact on the neurocognitive late effects, namely, the treatment related factors and the maternal educational level.

Recommendation for pediatric oncopsychological rehabilitation:

1. Examining paediatric cancer patients' illness representations clinicans can explore and change the maladaptive illness representations that affect the adaptation to the illness.

2. Psychological interventions based on strengthening patients' personal control and coherence feelings over their illness could improve the use of adaptive coping strategies and

quality of life outcomes. Pediatric cancer patients who feel they have greater control over their disease can cope with the treatment related stressors and show better quality of life indicators.

3. We also emphasise the importance of examinig the parental illness representations of paediatric cancer patients as these could affect the children's coping mechanism and adaptation to the illness

4. Based on our results we underline that Hungarian children treated for medulloblastoma suffer from long term cognitive impairment. The close monitoring of the cognitive functioning of children with medulloblastoma should play an important role at the beginning of their treatment and in their psychosocial rehabilitation as well.

5. We underline the need for early, preventive, corrective or therapeutic interventions to minimise the late academic difficulties among children with medulloblastoma.

The results of this dissertation highlight the importance of the illness representation of paediatric cancer patients, and the need to closely monitor their neurocognitive late effects to ensure a better quality of life and a more effective psychosocial rehabilitation.

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