**Intolerance of uncertainty in parents of childhood cancer survivors: a clinical profile analysis**

**Abstract**

**Purpose.** This research aimed to investigate the psychological adjustment related to the risk factor of intolerance of uncertainty in parents of childhood cancer survivors. **Design.** Participants were mothers (*N* = 45) and fathers (*N*= 16) of a childhood cancer survivor (from 4 until 6 years of cancer remission). Parents completed measures of intolerance of uncertainty and its associated factors (positive beliefs about worry, cognitive avoidance, rumination and problem solving), measures of psychological distress (anxiety, depression somatization and worries) and performed two Stroop tasks. **Findings.** A substantial subgroup of parents reported clinical levels of psychological distress and 64% reported a significant level of intolerance of uncertainty. Parents presented a high profile for intolerance of uncertainty (GAD profile) were those who had a high level of distress associated with ineffective psychological adjustment. **Conclusion.** The data are supportive of brief intervention to reduce intolerance of uncertainty. Sensitizing health care professionals to the identification of intolerance of uncertainty and its associated factors is essential for efficient intervention strategies.

**Abbreviations:** CCS: childhood cancer survivor; CCSs: childhood cancer survivors; IU: intolerance of uncertainty; GAD: generalized anxiety disorder; PTSS: Posttraumatic-stress symptoms.

**Keywords:** parents, child cancer survivor, intolerance of uncertainty, clinical profile and Stroop task.

**Background**

Over the past 40 years, medical advances in cancer treatment have increased survival rates for pediatric cancer and the average five-year survival rate is 80%in Belgium. **1** Late medical effects in childhood cancer survivors (CCSs) are well documented including second cancer as well musculoskeletal and cardiopulmonary impairment. **2,3** Concerning late psychological effects in CCSs studies observed mixed results with some studies reporting levels of psychological adjustment comparable to control, while others reported that a subgroup of CCSs displays an acute or chronic distress (e.g. depression, anxiety). **2,4**

The literature on psychological adjustment among parents of CCSs has reported increased levels of psychological distress such as posttraumatic-stress symptoms (PTSS), anxiety, depression sleep disturbances, fear of recurrence and lingering worry. **5** Conversely, some studies reported long-term positive consequences due to the child’s cancer disease such as resilience and positive changes (conceptualized as the posttraumatic growth (PTG)). **6**

Nevertheless, childhood cancer has long-lasting effects on parents and changes their surroundings towards uncertainty. To understand their life situation it is important to investigate how they cope with the aftermath of disease and how they regulate their behaviours through an uncertain context. **7, 8** Depending on the research focus, interest in risk factors that predict parents’ adaptation has been selective. Findings integrating personality risk factors (e.g. trait anxiety) have shown that these factors predict poor adjustment whereas protective personality factors (e.g. optimism) predict better adjustment. **7,9**

Regarding risk factors, no study has been carried out to examine the effect of intolerance of uncertainty (IU) on psychological and cognitive adjustment among parents of CCSs. IU is a personality trait whereby an individual has negative beliefs about uncertainty and uses several dysfunctional strategies (i.e. positive beliefs about worry, cognitive avoidance, rumination and negative problem orientation). **10, 11** IU involves a set of negative emotional, cognitive, and behavioral reactions to uncertain situations and it has been associated with various anxious disorders (generalized anxiety disorder (GAD)). **12** Cognitive studies also reported attentional biases and cognitive impairments (e.g. threat stimuli are detected faster than non-threat stimuli or difficulty to disengage attention from a threat stimulus compared to a non-threat stimulus).**13**

The aims were various: (1) describe the nature of long-term psychological late effects in parents of CCSs; (2) determine factors associated with/predicting long-term psychological late effects in parents of CCSs; (3) study the IU and its associated factors and (4) examine specific clinical profiles in order to assess the parental adjustment. We hypothesized that a high IU’s level could predict the clinical distress and specific cognitive impairments (attentional bias towards threat).

**METHOD**

***Procedures and Participants***

*Ethical approval statement*

The study took place in two hospitals treating childhood cancer in Liège (Belgium). Two Ethic commissions (hospital committee) approved all study procedures and recruitment materials (multicentric study) (the protocol was accepted in 2015). Date of diagnosis, stage of disease, type of cancer and treatments came from the two cancer registry databases.

*Participants*

Mothers (N= 45) and fathers (N=16) from 150 families of a CCS completed the study and 8 couples completed together the current study (53 cancer diagnoses). Parents who met the following criteria were eligible for the study: 1) child who had been diagnosed in remission since 4 years until 6 years; 2) neoadjuvant chemotherapy during treatments, 3) fluency in French speaking and 4) no previous evidence of mental illness. Exclusion criteria were diagnosis of cancer treated only by surgery, radiotherapy (with no adjuvant chemotherapy), benign tumor and non-French-speaking parents. Follow-up telephone calls were made, and letters sent to arrange data collection. Subsequent to exclusion criteria, there were 311 presumed-eligible participants among these 50.80% included therapeutic protocol (e.g. benign tumor, surgical resection or radiotherapy), 9.96% were children who were no longer followed at the hospital and contact could not be established (e.g. moving away), the remission range was exceeded or too recent (8.70%), the child died (8.36%), and the child had a relapse (2.57%).

***Measures***

Parents of CCS responded to several questionnaires and performed two Stroop tasks.

1. ***Psychological distress: anxiety, depression, worry and somatic symptoms***

The Hospital Anxiety Depression Scale (HADS) is a 14-item instrument assessing anxiety (7 items) and depression (7 items). Internal consistency of both subscales is excellent (anxiety Cronbach’s α =0.84-0.85; depression Cronbach’s α=0.79-0.81). **14**

The Penn State Worry Questionnaire (PSWQ) is a 16-item self-report instrument that assesses excessive and pathological worry; items are rated on a 5-point Likert Scale (i.e., ranging from “1:Not at all typical of me” until “5: Very typical of me”). PSWQ demonstrates good internal consistency (α = .84). **15** For the needs of the current study, we retained 10 of the 16 PSWQ items which were relevant to parents of a CCS. The instruction was modified and presented as following: “about the evolution of my child’s health”. Examples of the items include “ My worries overwhelm me” (item 1). Our exploratory results showed good internal consistency (Cronbach’s α =. 765 / 10 items) (PSWQ-R15). **16**

The Psycho Soma-Oncology Scale (PSOS) is an 8-item self-report instrument that assesses psychosomatic symptoms; items are rated on a 5-point Likert scale (i.e., ranging from “1:Not at all typical of me” until “5: Very typical of me”). The PSOS examines six dimensions: insomnia, loss of energy, weight, gastrointestinal symptoms, headaches and sexual disorders. Our exploratory reliability statistics observed sufficient internal consistency for the scale (Cronbach’s α = .657). **17**

1. ***The Intolerance of Uncertainty Model: intolerance of uncertainty, positive beliefs about worry, negative problem orientation, cognitive avoidance and rumination***

The Intolerance of Uncertainty Scale (IUS) is a 27-item self-report instrument that assesses beliefs about uncertainty. Items are rated on a 5-point Likert scale (i.e., ranging from “1:Not at all characteristic of me” until “5: Entirely characteristic of me”). IUS demonstrates excellent internal consistency (Cronbach’s α = .94). **18**

The Why Worry Questionnaire second version (WW-II) is a 25 item self-report measure containing five subscales of which each subscale assesses one type of positive belief about worry: (1) problem solving, (2) motivation, (3) emotion, (4) magical thought and (5) positive personality trait. WW-II demonstrates excellent internal consistency (Cronbach’s α = .93). **19**

The Negative Problem Orientation Questionnaire (NPOQ) is a 12-item self-report instrument on a 5-point Likert scale (i.e., ranging from “1:Not at all true of me” until “5: Extremely true of me”) that assesses dysfunctional cognitive pattern influencing the ability to solve daily life problems. NPOQ has excellent internal consistency (Cronbach’s α = .92). **20**

The Cognitive Avoidance Questionnaire (CAQ)is a 25-item measure of the tendency to use cognitive avoidance when dealing with threatening intrusive thoughts. CAQ contains five subscales, each of which assesses one type of avoidance strategy: (1) substitution, (2) transformation, (3) distraction, (4) avoidance and (5) thought suppression. CAQ has excellent internal consistency (Cronbach’s α = .95). **21**

The Mini-Cambridge-Exeter Repetitive Thought Scale (Mini-CERTS) is a 14-item scale assessing seven constructive (i.e., CET; “concrete experiential thinking”) and seven unconstructive (i.e., AAT; “abstract analytical thinking”) modes of thinking. The items were rated on a 1-4 scale (ranging from 1= almost never to 4 = almost always). Coefficients for the AAT (Cronbach’s α =. 75) and CET (Cronbach’s α =. 77) scales indicated acceptable internal consistency. **22**

1. ***Cognitive processes: Stroop tasks***

Two Stroop tasks (classic Stroop test and emotional Stroop test) were used in order to assess the effect of IU on cognitive processes. It is noteworthy that we did a pre-test for the selection of the words (positive, negative, coloured and neutral). Parents were instructed to target the colour of words both emotional and control (or neutral) while ignoring the semantic of the word. Emotional and neutral words in red, green, blue and yellow were displayed separately on a black computer screen. Inquisit software(version 4.0.9.0 Lab) was used on a computer (MacBook, OS X; version 10.11.15). **23** This neuropsychology software allows the encoding of a neuropsychological script (similar to the E-Prime program). Our design was built upon 130 trials (10 training trials and 120 experimental trials (30 coloured, 30 negative, 30 positive and 30 neutral stimuli)). Each target was presented during 500 milliseconds (ms.) and followed by a white screen during 250 ms. Examples of positive words were: [happy, wonderful], negative words (centred on parents of CCS) [tumour, bereavement], coloured [blue, green] and neutral [word, page]. To assess the attentional bias toward emotional words, we calculated the mean time reaction [RT] to target the colour of the emotional stimuli (positive and negative) and subtract it from the mean-time reaction to probe the neutral words. The term interference is used to describe the cognitive process that occurs during the emotional Stroop task. **24,25** Interference is calculated as follows:

* *CI*: Coloured interference =RT coloured words - RT neutral words (classic Stroop test)
* *NI*: Negative interference = RT negative words - RT neutral words (emotional Stroop task)
* *PI*: Positive interference = RT positive words - RT neutral words (emotional Stroop task)

**Analyses performed**

For descriptive statistics, the mean and standard deviation were calculated. For bivariate correlations Spearman coefficients were used. Rating scores of IUS, HADS and PSOS allow the establishment of four clinical profiles:

* *IU’s score: GAD profiles* (authors’ standard) = ***non-GAD*** (1 SD above the mean [score 0-48] = tolerance of uncertainty), ***moderate GAD*** (2 SD above the mean [score 49-77]) and ***severe GAD*** (3 SD above the mean [score > 78]). **18**
* *HADS’s subscales: anxious and depressive profiles* (authors’ standard) = ***non-depressed/non-anxious*** (< 7 HADS subscales) and ***depressed/anxious*** (≥ 7 HADS subscales). **14**
* *PSOS’s score: Somatic profiles* = ***non-somatic*** (1 SD above the mean [score 0-20]), ***moderate somatic symptoms*** (2 SD above the mean [score 21-27]) and ***severe somatic symptoms*** (3 SD above the mean [score > 28]).

Multivariate analyses of variance (MANOVA) were used with Bonferroni’s post-hoc tests for the time of cancer remission (3 conditions) and GAD profiles (3 conditions). The total score for PSOS (somatic symptoms), QIPS-R15 (worries) and HADS (anxiety/depression) were analyzed as dependent variables. The total score for IUS, WW-II, NPOQ, CAQ and Mini-CERTS (CET/ AAT) were examined as independent variables. Subsequently, stepwise regression procedures (exploratory procedure) are performed in order to determine factors associated with/predicting clinical distress in parents of CCSs. Lastly, two statistical restrictions were applied. Firstly, the use of a Spearman correlation test (rs) (unilateral significance) related to a non-normality result for some scales (Kolmogorov-Smirnov and Shapiro-Wilk tests). Secondly, the removal of mean scores for PI, NI and CI (Stroop tasks) due to a multicolinearity effect. **26** Statistical analyses were performed using SPSS for Mac, released 10.11.15 (version 20).

**Results**

***Sociodemographic and medical situation***

Mean age for mothers was 43.8 years and for fathers 46.25 years. Parents were married or living with a significant other (*n*= 53/61). The majority of parents had completed some post-secondary education (22 mothers, [78 %]; 6 fathers, [22%]).

Of the child cancer survivor, 37 (69.81%) were male and 24 cases were female (30.19%) (sex- ratio = 1.5). Cancer diagnoses were leukemias (14 [26.40%]), sarcomas (13 [24.50%]), lymphomas (7 [13.20%]), brain tumors (6 [11.32%]) and solid tumors (13 [24.52%]). Mean age of the CCS was 13 years (ET = 5.93) and was 7 years at the cancer diagnosis (ET = 5.51). Finally, it has to be noted that three groups of parents are established: (A) parents of CCS in remission for 4 years, (B) 5 years and (C) 6 years (see table 1).

Insert here Table 1

………………………………………………………………………………………………

***Psychological distress in parents of CCS***

About 40 % of parents (*n*= 24/61) presented symptoms of depression (score ≥ 7 points) with a higher trend for fathers (*n***father** 8 =/16 [50%]; *n***mother**16 =/45 [36%]). Concerning anxiety, 70 % of the sample (*n*= 43/61) showed a score beyond the threshold of 7 points on the HADS anxiety subscale with a higher trend for mothers (*n***mother** = 33/45 [73%]; *n***father** = 10/16 [63%]). As regards somatic symptoms, a majority of parents suffered from sleep disturbances and loss of energy with a higher trend for mothers (*n* **mother**= 8/45 [18%]) compared to fathers (*n***father**  =1/16 [6%]). Lastly, on average, parents of CCS had moderate to high extensive worries about the health of their child.

In addition, a correlation matrix was generated to assess the relationship between IU and distress components. IU was significantly correlated with anxiety (rs = .554, *p* = 0.000), depression (rs = .450, *p* = 0.000), worry (rs = .693, *p* = 0.000), and somatic symptoms (rs = .331, *p* = 0.005). This matrix revealed significant relationships between anxiety and depression (rs = .690, *p* = 0.000), anxiety and worry (rs = .528, *p* = 0.000) but also somatic symptoms and depression (rs = .543, *p* = 0.000).

***Clinical profile analyses***

Concerning the profile analysis, several findings were observed.

Firstly, results demonstrated that participants with a severe GAD profile (3 SD above the IUS’s mean) presented a high score for anxiety (*p* = 0.000), depression (*p* = 0.000), worries (*p* = 0.000) and somatic symptoms (*p* = 0.014) compared to moderate (2 SD above the IUS’s mean) or non-GAD profile (1 SD above the IUS’s mean). Results demonstrated no significant difference between non-GAD profile and moderate GAD profile except for worries (*p* = 0.002). In addition, a severe GAD profile was related to dysfunctional strategies. Indeed, parents with this profile were more intolerant of uncertainty (IUS), used more positive beliefs about worry (WW-II), presented a high negative problem orientation (NPOQ) and used more unconstructive thoughts (Mini-CERTS/UCT) compared to non-GAD or moderate GAD profiles. This trend is also observed in parents with an anxious or depressive profile (p< 0.05) (see Figure 1 and table 2).

Insert here Figure 1

………………………………………………………………………………………………

Secondly, findings reported no significant difference for clinical distress between the three remission groups (p>0.05). Nevertheless, a slight increase of distress was observed at the 5-year survival. Thirdly, no significant difference was observed for the gender both for clinical distress (HADS, PSWQ-R15 and PSOS) and the IU’s model (IUS, WW-II, CAQ, NPOQ and Mini-CERTS) (p>0.05) (see table 2).

Insert here Table 2

………………………………………………………………………………………………

Lastly, concerning the two Stroop tasks, CI [RT colour words - RT neutral words] and NI [RT negative words - RT neutral words] (ms.) were slightly higher than positive interference (PI). The profile analysis reported no significant difference (p> 0.05) between the four profiles (i.e. GAD, anxious, depressive or somatic profile). Nevertheless, a slower reaction time was observed for both depressive and GAD profiles. In addition, a faster reaction time was observed for both anxious and somatic profiles (see table 3).

………………………………………………………………………………………………

Insert here Table 3

***Predictors of psychological distress***

*A. Depression*

In order to examine possible predictors of depressive symptoms, stepwise linear regression analyses were conducted. Results are displayed in table 4. Factors included in the model were: IUS, NPOQ, CAQ, WW-II, Mini-CERTS, PI, NI and CI. Two models are displayed. Note that we have chosen the strongest model (R2) with significant predictors (p<0.05). The regression model revealed a significant model for a significant portion of the variance concerning the depression score (R2 = .407). The regression line for depressive symptoms was equal to -2.601 + .160 (NPOQ) + .071 (IUS) + (2nd model). The negative problem orientation (*β* = .160, *p* = 0.018) and intolerance of uncertainty (*β* = .071, *p* = 0.021) reached statistical significance as predictors for depression (F (2,58)= 19.912, p= .000). In other words, a negative problem orientation and the intolerance of uncertainty contribute to predicting the level of depressive symptoms. In addition, symptoms of depression were significantly correlated with positive beliefs about worry (rs= .379, p<. 01) and unconstructive thoughts (rs= .350, p<. 01) (see table 4).

Insert here Table 4

………………………………………………………………………………………………

*B. Anxiety*

In order to examine possible predictors of anxious symptoms, stepwise linear regression analyses were conducted. Results are displayed in table 5. Factors included in the model were: IUS, NPOQ, CAQ, WW-II, Mini-CERTS, PI, NI and CI. Four models are displayed. Note that we have chosen the strongest model (R2) with significant predictors (p<0.05). The regression model revealed a significant model for a significant portion of the variance concerning the anxiety score (R2 = .514). The regression line for anxious symptoms was equal to -.327+ .228 (NPOQ) + .079 (WW-II) (4th model). The negative problem orientation (*β* = .228, *p* = 0.000) and positive beliefs about worry (*β* = .079, *p* = 0.001) reached statistical significance as predictors for anxiety (F (2,58)= 30.642, p=. 000). In other words, a negative problem orientation and positive beliefs about worry contribute to predicting anxious symptoms. In addition, symptoms of anxiety were significantly correlated with intolerance of uncertainty (rs= .554, p<. 01) and unconstructive thoughts (rs= .507, p<. 01) (see table 5).

Insert here Table 5

………………………………………………………………………………………………

*C. Somatic symptoms*

In order to examine possible predictors of somatic symptoms, stepwise linear regression analyses were conducted. Results are displayed in table 6. Factors included in the model were: IUS, NPOQ, CAQ, WW-II, Mini-CERTS, PI, NI and CI. One model is displayed. Results demonstrated a weaker regression model (R2 = .216) compared to depression (R2 = .407) and anxiety (R2 = .514). The regression line for somatic symptoms was equal to 6.179 + .314 (NPOQ). The negative problem orientation (*β* = .314, *p* = 0.000) reached statistical significance as a predictor for somatic symptoms (F (2,58)= 16.294, p=. 000). In other words, a negative problem orientation contributes to predicting somatic symptoms. In addition, somatic symptoms were significantly correlated with unconstructive thoughts (rs= .356, p<. 01) and cognitive avoidance (rs= .341, p<. 01) and intolerance of uncertainty (rs= .331, p<. 01) (see table 6).

Insert here Table 6

………………………………………………………………………………………………

*D. Worry*

In order to examine possible predictors of worry, stepwise linear regression analyses were conducted. Results are displayed in table 7. Factors included in the model were: IUS, NPOQ, CAQ, WW-II, Mini-CERTS, PI, NI and CI. Five models are displayed. Note that we have chosen the strongest model (R2) with significant predictors (p<0.05). The regression model revealed a significant model for a significant portion of the variance concerning the worry score (R2 = .688). The regression line for worry was equal to - .950 + .123 (IUS) + .119 (WW-II) + .257 (NPOQ) + .315 (CERTS/CT) + .028 (PI) (5th model). Intolerance of uncertainty (*β* = .123, *p* = 0.014), positive beliefs about worry (*β* = .119, *p* = 0.004), negative problem orientation (*β* = .257, *p* = 0.006), constructive thoughts (*β* = .315, *p* = 0.015) and positive interference (*β* = .028, *p* = 0.040) reached statistical significance as predictors for worry (F (2,58)= 24.269, p=. 000). In other words, intolerance of uncertainty, positive beliefs about worry, negative problem orientation, constructive thoughts (type of rumination) and positive interference contribute to predicting parental worries. In addition, the worry was significantly correlated with unconstructive thoughts (rs= .453, p<. 01) and cognitive avoidance (rs= .360, p<. 01) (see table 7).

Insert here Table 7

………………………………………………………………………………………………

In a nutshell, results demonstrated the major issue of negative problem orientation (NPOQ) in the development of various symptoms such as anxiety, depression, somatic symptoms or extensive worry. Negative problem orientation is observed as a set of dysfunctional cognitions that influences one’s ability to effectively solve daily life problems. Therefore, parents who reported a negative problem orientation seem to present a higher risk for clinical distress.

**Discussion**

After battling the cancer with their child, many parents endure numerous difficulties throughout their lives despite the cancer’s remission. Parents must provide emotional and psychological support to their CCSs, while simultaneously processing their own worries (e.g. late effects of cancer treatment, relapse) and emotions. Parents must also face the uncertainty. The conceptualization of IU and its associated difficulties provides a framework for understanding the ongoing psychosocial sequelae of parents. To the best of our knowledge, this is the first study investigating the risk factor of IU in parents of CCS. Results demonstrated that IU is common in both mothers and fathers (64 % of the sample) and higher compared to a clinical sample of adults. **12** Whereas previous literature on parents of CCSs has looked primarily at anxiety and/or depression, findings of the current study reported the existence of IU as a risk factor increasing the clinical distress (e.g. anxiety, worry) and dysfunctional behaviours (e.g. rumination, cognitive avoidance). Concerning the clinical distress, results demonstrated that the 5-year of survival remained an important milestone for parents where clinical distress was significant both for mothers and fathers. Other studieshave already reported significant symptoms of distress at that time (i.e. 5-year survival has been the primary benchmark of therapeutic success for parents and physicians). **4,5**

**Limitations and future research directions**

This study has several limitations that may have influenced the generalizability of these results. First, the quantitative study does not allow targeting other clinical variables (e.g. trauma, family and social factors). Indeed, the number of other difficulties will differ among parents, as well the interpretation of these events (e.g. perception, interpretation and coping). Second, although all analyses were adequately powered (stepwise regressions, post-hoc tests), the sample size was modest in comparison to other studies. **2,5** Third, the modest internal consistency of “The Penn State Worry Questionnaire Revised” (PSWQ-R15) and “The Psycho Soma-Oncology Scale” (PSOS) may have influenced the findings. **26** It is necessary to readjust these two scales in a future research. Lastly, it would be advantageous to develop more studies including neurocognitive tasks. Regrettably, few studies focused on understanding the activated cognitive operations (i.e., attention and working memory) and their issues for parents of CCSs. Our results reported the relationship between IU and an attentional orientation towards threat. Future research should aim to clarify the nature of relationships between IU and cognitive impairment, together with potential mediating and moderating factors such as negative problem orientation and cognitive avoidance.

**Clinical implications**

In summary, our findings indicate that a substantial subgroup of parents of CCS report long-term negative psychological effects. This data supports the utility of IU and its associated factors in understanding clinical distress in parents of CCSs. This study raises awareness of the need for ongoing monitoring of IU among parents of CCS; and opportunities for future research, incorporating parent interviews and intervention development. Therefore, these results highlight the necessity to identify parents who are at risk for IU at an early stage of the cancer management in order to propose personal psychological interventions (e.g. problem solving therapy), to adapt certain cognitive strategies (e.g. excessive worries), to develop resilience, and to promote “positive growth” for parents.While strategies and interventions to minimize the child’s distress have become part of comprehensive medical care in pediatrics, it also becomes urgent to develop research into parents of CCSs in order to: [1] train the medical staff to identify the serious issue of parental IU; [2] detect clinical profiles (e.g. GAD) and [3] provide them with a personalized psychological intervention.

This would allow vigilance of the medical staff in detecting parents’ distress and could defuse their descent into a vicious circle of hypervigilance and extensive worry created by intolerance of uncertainty (IU).