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Determinants of impairments in functioning, fatigue, and participation ability in pediatric brain tumor survivors

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Abstract

Background. Pediatric brain tumor survivors (PBTS) experience disease- and treatment-related sequelae. We aimed to investigate the occurrence of participation limitations, impairments in functioning, fatigue, and the association between patient, tumor- and treatment-related factors and these outcomes.

Methods. Children (4–18 years) after treatment for a brain tumor between 2005 and 2014 at the Erasmus Medical Center, Rotterdam, the Netherlands, were eligible. The parent-reported Child and Family Follow-up Survey developed to measure participation and impairments in functioning in youth with acquired brain injury, was used. Fatigue was assessed using the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale. Associations with patient, tumor- and treatment-related factors were explored using univariable analyses.

Results. Ninety-one PBTS (median age: 11.3 years [range: 9.5–14.1], time since treatment: 3.9 years [range: 4–6.2]) were included (response rate: 55%). Participation limitations were reported in 53% and were associated with impairments in functioning (15–67%) ($P \leq .01$) and fatigue ($P \leq .03$).

Parent- and child-reported fatigue was increased compared to normative values ($P \leq .02$). History of hydrocephalus was associated with increased fatigue ($P \leq .04$). Younger age at diagnosis and longer time since diagnosis were associated with impairments in functioning and cognitive fatigue ($P < .05$).

Participation limitations, impairments in functioning and fatigue were similar in PBTS who were <3 or ≥3 years since completion of treatment.

Conclusion. More than half of PBTS reported limited participation ability, which is associated with impairments in functioning and fatigue. The complication hydrocephalus seems to lead to more fatigue. Participation limitations, impairments in functioning and fatigue appear not to diminish in the longer term.

Key Points

- Age-expected participation appears to be limited in over 50% of pediatric brain tumor survivors.
- Pediatric brain tumor survivors with increased general and cognitive fatigue were more likely to report participation limitations.
- Participation limitations, impairments in functioning and fatigue do not seem to diminish over time.

Importance of the Study

Pediatric brain tumor survivors (PBTS) are at risk of disease- and treatment-related sequelae, which can complicate their ability to participate in daily life. In this study, we found that more than 50% of PBTS (aged 4–18 years) reported participation limitations, that impairments in functioning (cognitive, physical, psychological, and sensory) were frequently experienced (15–67%), and that both parent- and child-reported general and cognitive fatigue were increased. These problems seemed not to have diminished after ≥3 years since treatment. This is one of the first studies to also assess fatigue in PBTS <12 years of age, which is of importance because we were able to show that increased fatigue was associated with limited participation. These results underline the importance of addressing the problems of fatigue early in follow-up after brain tumor treatment, and to offer structured interventions that may mitigate these problems and improve participation ability in daily life.

Brain tumors are the most common pediatric solid tumors and represent the second most frequently diagnosed malignancies in childhood.[1] Currently, an overall 5-year survival rate of approximately 75% is reached.[2] Improvements in neuro-imaging, treatment modalities, and risk stratification as well as supportive care, have resulted in a growing population of pediatric brain tumor survivors (PBTS). However, this improvement is accompanied with various disease- and treatment-related sequelae,[3–6] which can have serious implications on participation in daily life activities and meaningful life situations in various settings.[7]

The effect of a pediatric brain tumor and its treatment on different aspects of functioning has been investigated, but either in small sample sizes, in cohorts of adult survivors or focusing predominantly on neuro-behavioral disorders.[7–13] Results therefore vary and are sometimes contradictory. For example, more neurocognitive problems have been reported in children with an infratentorial located tumor compared to those with a supratentorial tumor.[14] In contrast, a different study associated a supratentorial location with more severe disabilities in children treated for a low-grade astrocystoma.[15] This was supported by another study, in which a supratentorial tumor location, recurrent neurosurgery, shunt revisions, and chemotherapy were associated with major disabilities.[3]

Fatigue is another regularly reported short- and long-term side effect. An increase in fatigue was reported in PBTS one year after completion of treatment.[16] Further into survivorship, fatigue remains a problem with 13–15% of adolescent and adult PBTS having severe fatigue complaints.[17,18]

The extent of daily life participation in PBTS in the subsequent years of childhood has not been investigated nor have influencing factors been systematically recognized. It also remains unclear, if the severity of participation limitations, impairments in functioning and fatigue, increase, decrease, or stabilize after therapy cessation. Early identification of PBTS who are at risk of participation limitations and fatigue may aid early and appropriate rehabilitation care.

Hence, the aims of this study were to investigate: the occurrence of self-reported participation limitations, impairments in functioning and fatigue in childhood PBTS in the short and long term. In addition, to identify potential patient, tumor- and treatment-related determinants for participation limitations, impairments in functioning and fatigue, and to investigate the associations between impairments in functioning and fatigue, and participation.

Methods

Study Design and Participants

In this cross-sectional study, all PBTS (aged 4–18 years) who were diagnosed between January 2005 and June 2014 at the Erasmus Medical Center Rotterdam (EMC) – Sophia Children's Hospital, Rotterdam, the Netherlands, were eligible and actively recruited. Medical treatment had to be completed prior to enrollment in the study, or children had to be under active surveillance with stable neurology, no tumor growth or recurrence, at time of the study. An overview of the study design is schematized in Figure 1.

Ethical approval of the study was obtained from The Medical Ethics Committee of the EMC Rotterdam (MEC-2014-197). Written informed consent according to the Helsinki agreement was obtained from all participating parents, and from children aged ≥12 years.[19] This study was conducted between June 2014 and March 2015.

Data Collection and General Information

Information regarding demographics and brain tumor-related characteristics were obtained from the medical records and the pediatric oncology database of the EMC. The following information was collected: sex, age at study time, age at diagnosis, type of brain tumor, presence of neurofibromatosis type 1 (NF-1) as underlying predisposing condition, date of last treatment, tumor grade (according to the World Health Organization, grade I/II = low-grade, grade III/IV = high-grade), tumor location (infratentorial or supratentorial), type of treatment (neurosurgery, radiotherapy, chemotherapy, or active surveillance). Neurosurgical treatment was categorized as radical or partial resection of the tumor. Details on surgical procedures for treatment of hydrocephalus were collected, ie endoscopic third ventriculostomy or ventriculoperitoneal

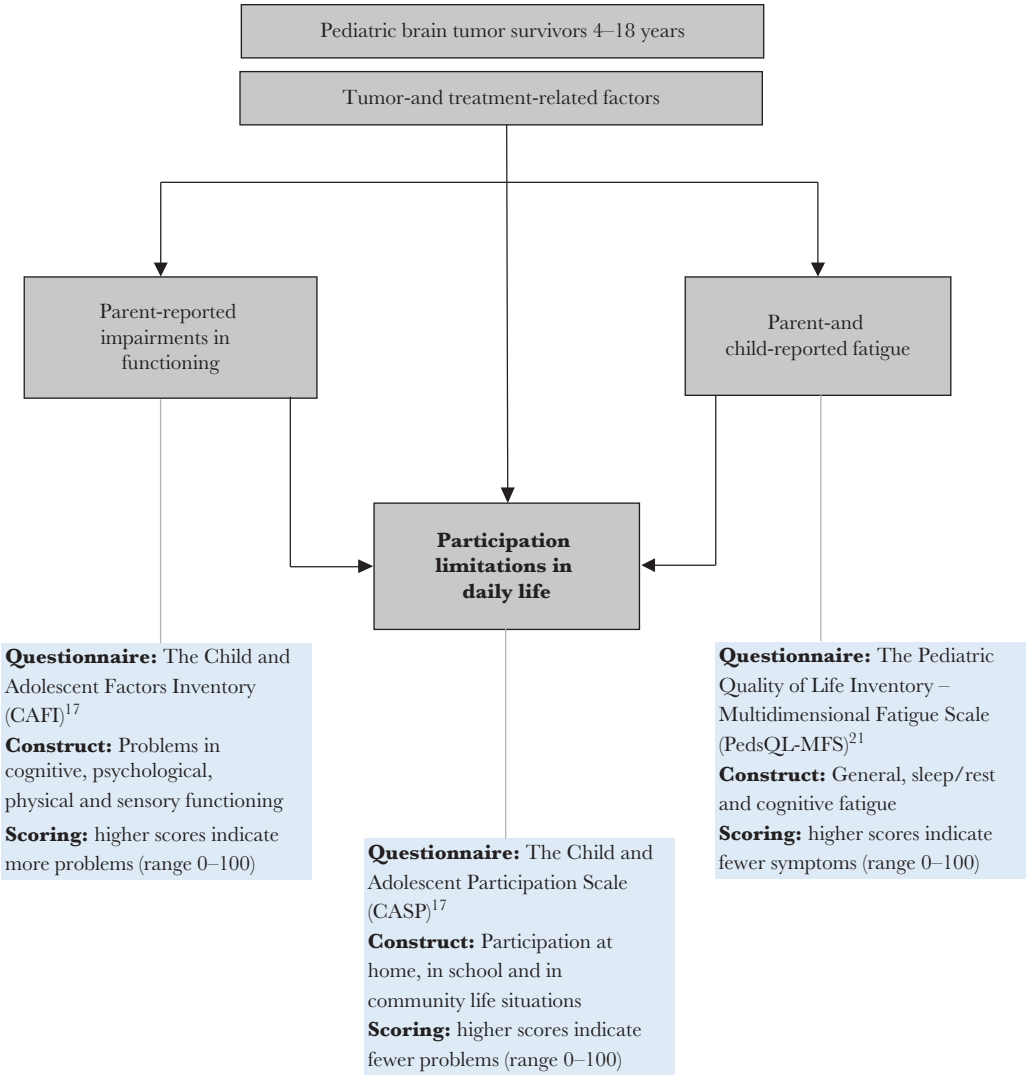

Figure 1. Overview of study design.

shunt placement. Time since end of treatment was defined as the time since the last day of chemo/radiotherapy administration, last surgical procedure or since the decision for a surveillance approach, until the day the questionnaires were filled out. We dichotomized time since end of treatment at <3 and ≥3 years, respectively short- and long-term.

Data were collected using questionnaires that were sent by regular mail. Paper forms were filled out by parents and children at home. If a child version of a questionnaire was not returned, only the parental version was included.

Outcome Measures

Participation.—The Dutch parental version of the Child and Adolescent Scale of Participation (CASP) was used to measure participation, which is part of the Child and Family Follow-up Survey (CFFS).[20] This questionnaire has been specifically developed to assess outcomes in children and adolescents (4–21 years) with acquired brain injury.[21] The CASP is a 20-item questionnaire and measures the extent of participation and limitations in home, in school and community life situations and activities, on a 4-point scale (unable, very limited, somewhat limited, or age-expected). Scores for each item are summed and divided by the maximum possible score, the results multiplied by 100, give a final score between 0 and 100, with a higher score indicating a better participation level (Figure 1). The Dutch version of the CFFS (including CASP) has been validated in youth with acquired brain injury, and was found to have good to excellent internal consistency.[20] In accordance with previous studies, we defined that a CASP score of ≥97.5 indicates "age-expected participation", subsequently a CASP score below 97.5 refers to "limited participation", and a score ≤81 indicates "very limited participation" (Supplementary Table 1).[22,23]

Impairments in functioning.—The Child and Adolescent Factors Inventory (CAFI), which is also part of the CFFS,

was used to assess parent-reported impairments in functioning.[20] The CAFI consists of 17 items and focuses briefly on health-related impairments in cognitive, psychological, physical, and sensory functions. Each impairment is rated on a 3-point scale, (major, minor, or no problem) summed up to a total score. A lower score indicates a better level of functioning (0–100) (Figure 1). One previous study divided CAFI scores based on the median CAFI score in their cohort of children with acquired brain injury (≤40 indicated a low score).[23] No studies using a cutoff point for CAFI are available.

Fatigue.—The Dutch version of the Pediatric Quality of Life Inventory (PedsQL) – Multidimensional Fatigue Scale (MFS) was used to assess fatigue-related problems.[24,25] This questionnaire consists of three scales: general fatigue, sleep/rest fatigue, and cognitive fatigue (Figure 1). Higher scores indicate less fatigue. We used the parental versions for children aged 2–4, 5–7, 8–12, 13–18 years, and self-report versions for children aged 8–12 and 13–18 years, of which Dutch norm-references are available.[24] Previous studies showed that the internal consistency of the Dutch version of the PedsQL–MFS was satisfactory, test-retest reliability was good and the inter-observer reliability varied from moderate to excellent.[24]

Statistics

The frequency of participation limitations (CASP) and major/minor impairments in functioning (CAFI) were calculated in percentages.

Fatigue levels (PedsQL–MFS scores) were compared to normative values[24] using two-sample *t*-tests. In small groups (n = <25), the Mann-Whitney *U* test was performed. Possible confounding by age and sex distributions between the normative values and our cohort was assessed.

To quantify the difference in PedsQL-MFS between our cohort and the normative values we used Cohen's d effect sizes, calculated by dividing the difference in mean scores of our cohort and the normative cohort by the standard deviation of the normative cohort. Effect sizes between 0.2 and 0.5 were considered small, effect sizes between 0.5 and 0.8 moderate, and effect sizes ≥0.8 large.[26]

The CASP, CAFI, and PedsQL-MFS scale scores were compared in PBTS who were <3 and ≥3 years since end of therapy, using Mann-Whitney *U* tests or two-sample *t*-tests, based on the (non-)normally distribution of the data.

To identify potential patient, tumor- and treatment-related determinants, chi-squared or Fishers exact tests were used to assess associations between the following independent variables: sex, tumor grade, tumor location, cranial radiotherapy, chemotherapy, active surveillance, partial or radical resection, procedure for hydrocephalus treatment, NF-1, and the dependent variables: "limited participation" and "very limited participation" (CASP). Two-sample *t*-tests were used to explore these associations with age at study time, age at diagnosis, and time since diagnosis.

Furthermore, to explore associations between the aforementioned independent variables and impairments in functioning (CAFI) and fatigue (Parent- and self-reported PedsQL-MFS scores), we used the Mann-Whitney *U* tests and two-sample *t*-tests, respectively.

To investigate whether impairments in functioning and fatigue were associated with participation, we tested whether the occurrence of impairments (CAFI) and fatigue (PedsQL-MFS), in children with limited participation differed from those with age-expected participation, using Fishers exact tests and two-sample *t*-tests respectively. In addition, we compared the PedsQL-MFS scores of children with limited and age-expected participation to the Dutch normative values, separately as well.

Level of significance for all analyses was set at *P*-value below .05. All analyses were performed using software package R Statistics™ Version 1.1.456 for Windows.

Results

Cohort

One hundred and fifty-one children who were diagnosed with a brain tumor between January 2005 and June 2014 at the EMC were eligible to participate in this study. After exclusion of children who were lost to follow-up or nonresponders, ninety-one PBTS participated (55%) (Figure 2*: Flow diagram*).

The included survivors had a median age of 11.3 years (interquartile range [IQR]: 9.5–14.1) at study time, and a median of 3.9 years (IQR: 2–6.2) since end of treatment or decision for active surveillance (8.8%). Forty-nine (53.8%) were boys, the majority had a low-grade tumor (80.2%) and astrocytoma was the most frequent type of tumor (37.4%). Complete characteristics are described in Table 1.

Responders (n = 91) did not differ significantly from the nonresponders (n = 74) with regard to sex, age at study inclusion, age at diagnosis, time since diagnosis, tumor grade, and location ($P \geq .05$).

Participation (CASP)

The median total score reported on the CASP was 95.3 (IQR: 82.5–100), with median scores of 95.8 (IQR: 87.5–100) for participation at home, 93.6 (IQR: 79.7–100) for participation in the community, 100 (IQR: 90–100) at school, and 95 (IQR: 80–100) for home and community living activities (Table 2).

Participation was limited (CASP < 97.5) in 47/88 (53.4%) children; 51.1% was experiencing limitations in participation at home and in the community, 46.7% at school and 52.8% in home and community living activities (ie, household activities, managing a daily schedule) (Results on item level are shown in Supplementary Figure 1). Very limited participation (CASP ≤ 81) was reported in 19/88 (21.6%) of the cohort. The remaining 41 children (46.6%) had age-expected participation.

In children with limited participation the frequency of special education needs was higher compared to children with age-expected participation (46.8% vs 13.5%, P <.01).

The extent of participation was no different in children who were <3 or ≥3 years since their last treatment ($P \geq .19$) (Table 2).

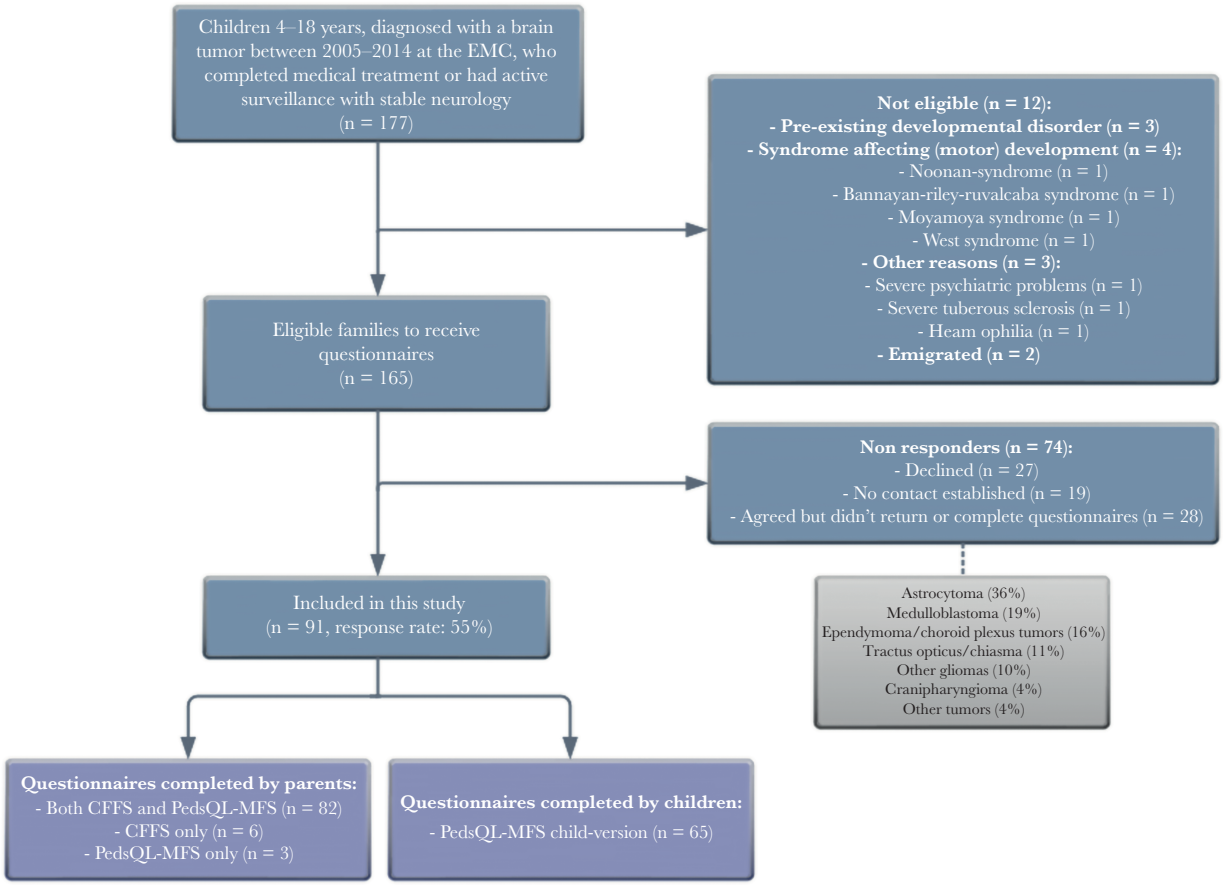

Figure 2. Flow diagram of participant inclusion and response. Abbreviations: CFFS, Child and Family Follow-up Survey; PedsQL-MFS, Pediatric Quality of Life Inventory – Multidimensional Fatigue Scale.

Impairments in Cognitive, Psychological, Physical, and Sensory Functioning (CAFI)

The median total score reported on the CAFI was 47.1 (IQR: 39–57). Frequencies of the self-reported impairments in cognitive, psychological, physical, and sensory functioning are shown in detail in Supplementary Figure 2. Of the 17 items measured by the CAFI the following three were a minor or major problem in >50% of the children: attention/concentration (67%), movement (balance, coordination, muscle tone) (57%), and strength/energy level (51%).

CAFI scores were no different in children who were <3 or ≥3 years after cessation of treatment ($P = .16$) (Table 2).

General, Sleep/Rest, and Cognitive Fatigue (PedsQL-MFS)

General and cognitive fatigue in the total cohort were increased in both the parent- and child-reports compared to normative values of Dutch children ($P \leq .02$), sleep/rest fatigue was also increased but only in parent-reports ($P = .01$).

Differences in subscales between the three age-specific versions (respectively 5–7 years; 8–12 years; 13–18 years) were observed. In 5–7 year old children, parents reported only more general fatigue ($P = .03$), but in 8–12 year old children, parents reported increased fatigue on all three subscales (general, sleep/rest, and cognitive) compared to normative values ($P \leq .02$). Self-reported child scores in this age group also indicated more general and cognitive fatigue ($P \leq .01$). In 13–18 year old children, parents reported more cognitive fatigue ($P \leq .02$). However, there were no significant differences on the self-reported scales of children in this age group ($n = 31$), a moderate effect size of –0.52 was found for cognitive fatigue ($P = .09$). Complete results on the PedsQL-MFS scales and comparison to normative values are presented in Table 3, with the exception of the age group 2–4 years, as there was only one child aged <5 years old.

PedsQL-MFS scores were no different in children who were <3 or ≥3 years after last treatment ($P = .45$) (Table 2).

Potential Patient-, Tumor- and Treatment-related Determinants of Participation, Impairments in Functioning, and of Fatigue

Participation.—Active surveillance was the only factor associated with participation and had a

Table 1. Characteristics of Pediatric Brain Tumor Survivors (PBTS) ($n = 91$)

	Median	Interquartile Range
Age at study time, years	11.3	9.5–14.1
Age at diagnosis, years	5.9	3.8–9.2
Time since diagnosis, years	4.4	2.4–6.7
Time since end of treatment,[a] years	3.9	2.0–6.2
	No.	%
Sex		
Boy	49	53.8
Girl	42	46.2
Type of brain tumor		
Astrocytoma	34	37.4
Ependymoma and choroid plexus tumors	10	11
Medulloblastoma	9	10
Tractus opticus/chiasma	8	8.8
Other gliomas	7	7.7
Craniopharyngioma	6	6.6
Other tumors	11	12.1
Unidentified	6	6.6
Tumor grade[b]		
High-grade	18	19.8
Low-grade	73	80.2
Tumor location		
Infratentorial	46	50.5
Supratentorial	45	49.5
Treatment modalities		
Neurosurgery	65	71.4
Radical or partial resection	13	14.3
Procedure for treatment of hydrocephalus[c]	28	31.9
Chemotherapy		
Cranial radiotherapy	37	33
Active surveillance	8	8.8
Combination of radio/chemotherapy and neurosurgery	37	40.6
Neurofibromatosis type 1		
Yes	13	14.3
No	78	85.7
Type of education		
Regular education	61	67
Special education	28	30.8
Not attending school	2	2.2

[a]End of treatment was defined as last the day of chemo/radiotherapy administration, time since surgical procedure, or time since decision for active surveillance.
[b]Grade I/II equals low-grade, grade III/IV equals high-grade.
[c]Endoscopic third ventriculostomy or ventriculoperitoneal shunt placement.

positive effect on age-expected participation (2.1% vs 18.4%, $P = .02$). Sex, age at study time, age at diagnosis, time since diagnosis, time since end of treatment, tumor location, tumor grade, type of received treatment (chemotherapy, cranial radiotherapy, or neurosurgery), and underlying predisposition (NF-1) were not associated with limited or very limited participation (Supplementary Tables 2 and 3).

Table 2. CASP, CAFI, CASE, and PedsQL-MFS Scores in Total PBTS Cohort and in Subgroups (<3 or ≥3 Years Follow-up)

	Total Cohort			<3 Years Since Last treatment[a]			≥3 Years Since Last Treatment[a]			
	N	Mean	Median (IQR)	*N*	Mean	Median (IQR)	*N*	Mean	Median (IQR)	*P*[b]
CASP total score (range 0–100)c	85	90.4	95.3 (82.5–100)	31	91.2	95.3 (83–100)	46	89.4	93.9 (81–100)	.62
Home participation	88	91.7	95.8 (87.5–100)	32	93.7	97.9 (87.5–100)	48	90	95.4 (83.3–100)	.25
Community participation	88	88.1	93.6 (79.7–100)	32	88.5	96.9 (79.7–100)	48	87.1	93.8 (75–100)	.63
School participation	87	93.6	100 (90–100)	32	94.9	100 (93.8–100)	47	92.3	95 (85–100)	.19
Home and community living activities	86	87.3	95 (80–100)	31	88.4	95 (80–100)	47	86.1	93.8 (77.5–100)	.43
CAFI total score (range 0–100)[d]	88	48.9	47.1 (39.2–56.9)	32	46.9	44.1 (37.3–55.4)	48	51	48 (40.7–59.3)	.16
PedsQL-MFS parent-form (range 0–100)[c]										
Total fatigue	85	67.9	66.7 (54.2–84.7)	32	68.2	70.8 (51–87.5)	45	65.6	65.3 (54.2–80.6)	.59
General fatigue	85	65.3	66.7 (50–87.5)	32	65.8	64.6 (49–87.5)	45	63.2	62.5 (50–75)	.65
Sleep/rest fatigue	86	78.5	83.3 (66.7–91.7)	32	79.3	83.3 (65.6–95.8)	46	77.2	79.2 (66.7–91.7)	.82
Cognitive fatigue	86	59.5	60.4 (34.4–82.3)	32	60.6	62.5 (36.5–80.2)	46	55.7	52.1 (33–78.1)	.45
PedsQL-MFS child-form (range 0–100)[c]										
Total fatigue	62	70.1	68.8 (57.3–84.4)	24	67.5	70.1 (51–76.7)	36	71.3	68.1 (59.4–85.1)	.46
General fatigue	62	73.1	75 (60.4–91.7)	24	67.4	70.8 (50–87.5)	36	75.4	75 (66.7–91.7)	.19
Sleep/rest fatigue	64	73.6	75 (62.5–87.5)	24	72.6	75 (60.4–89.6)	38	74.1	72.9 (63.5–87.5)	.77
Cognitive fatigue	65	64.2	62.5 (41.7–87.5)	24	62.7	58.3 (41.7–87.5)	38	63.6	64.6 (43.8–83.3)	.89

Abbreviations: CASP, Child and Adolescent Participation Scale; CAFI, Child and Adolescent Factors Inventory; PedsQL-MFS, Pediatric Quality of Life Inventory – Multidimensional Fatigue Scale; PBTS, Pediatric brain tumor survivors; IQR, Interquartile range.
[a]Last treatment is defined as last day of chemo/radiotherapy administration, or day of surgery. Children under active surveillance (no treatment) are excluded from this analysis ($n = 8$).
[b]Mann-Whitney *U* tests based *P*-value for difference in subgroup scores CASP, CAFI, and CASE (<3 or ≥3 years since last treatment); Two-sample *t*-tests were used for PedsQL-MFS scores.
[c]Higher scores indicate less problems.
[d]Lower scores indicate less problems.

Impairments in cognitive, psychological, physical, and sensory functioning.—In children who were aged <6 years at diagnosis more impairments in cognitive, psychological, physical, and sensory functioning were reported (median CAFI score: 51 vs 43, $P \leq .01$), compared to PBTS who were ≥6 years of age at diagnosis.

Also in children who had been diagnosed ≥5 years ago, more impairments in functioning were reported (median CAFI score: 51 vs 43, $P = .04$) compared to those who had been diagnosed <5 years ago. The remaining factors were not associated with self-reported impairments in functioning (Supplementary Table 4).

General, sleep/rest, and cognitive fatigue.—A history of hydrocephalus was associated with increased general fatigue, as reported by parents (mean: 50 vs 67.1, $P = .02$) and also by children themselves (mean: 59.7 vs 75.3, $P = .04$), compared to children who did not undergo such a procedure. Parents of children who had a history of hydrocephalus also reported increased sleep/rest fatigue (mean: 66.3 vs 80.5, $P = .02$).

Children who had NF-1 reported more general fatigue compared to those without NF-1 (mean: 54.2 vs 75.1, $P = .02$).

Increased cognitive fatigue was reported by parents of children that had a radical or partial resection, compared to children who did not have resections (mean: 55.1 vs 70.7, $P = .02$) (this is most likely explained by the location of tumor which would not need or allow a resection rather than the resection per se; 30% of these children had optic pathway gliomas).

Parents of children who were ≥5 years since diagnosis, reported more cognitive fatigue compared to those who were <5 years since that time (mean: 51. vs 65.7, $P = .02$). Children (self-reported) who were aged <6 years at diagnosis reported more cognitive fatigue in comparison with children who were ≥6 years of age at diagnosis (mean: 56 vs 69.4, $P = .04$). Also, those who were treated with chemotherapy reported more cognitive fatigue, as opposed to children who had not received chemotherapy (53.9 vs 67.9, $P = .04$). There were no associations between the remaining factors and the three fatigue categories (parent-report nor children-report) in this cohort of PBTS (Table 4).

Table 3. PedsQL Multidimensional Fatigue Scale Scores in PBTS and Comparison to Children from the General Dutch Population

	Young Child (5–7 years)					Child (8–12 years)					Adolescent (13–18 years)					Total sample				
	N	Mean	SD	*P*	d[a]	N	Mean	SD	*P*	d[a]	N	Mean	SD	*P*	d[a]	N	Mean	SD	*P*	d[a]
Child report																				
Total fatigue	–					31	67.3	17.7	**.00****	−0.91	31	72.9	18.4	.50	−0.20	62	70.1	18.1	**.00***	−0.55
General fatigue	–					32	71.4	21.8	**.00***	−0.88	31	74.9	20	.63	−0.13	63	73.1	20.8	**.02**	−0.46
Sleep/rest fatigue	–					33	72.7	17.2	.11	−0.32	31	74.6	20	.48	0.19	64	73.6	18.5	.70	−0.07
Cognitive fatigue	–					34	59.7	25.4	**.00***	−0.84	31	69.2	24.1	.09	−0.52	65	64.2	25.1	**.00****	−0.71
Parent report																				
Total fatigue	13	73.5	20.8	.13	−0.84	41	64.8	20	**.00****	−1.29	31	69.7	21	**.02**	−0.68	85	67.9	20.5	**.00****	−0.99
General fatigue	13	69.2	21.6	**.03**	−1.23	41	61.3	25.3	**.00****	−1.50	31	69.1	23.3	.06	−0.54	85	65.3	24.1	**.00****	−1.05
Sleep/rest fatigue	13	83.0	17.4	.36	−0.39	42	78.8	16.9	**.02**	−0.51	31	76.2	22.1	.27	−0.31	86	78.5	18.9	**.01**	−0.40
Cognitive fatigue	13	68.3	26.4	.13	−0.49	42	53.6	29.3	**.00****	−1.14	31	63.7	26.4	**.00***	−0.85	86	59.4	28.2	**.00****	−0.97

Abbreviations: PedsQL, Pediatric Quality of Life Inventory; PBTS, Pediatric brain tumor survivors.
Note: Higher scores indicate less fatigue.
P-values at Mann-Whitney U or two-sample *t*-test; level of significance at $P \leq .05$, $^{*}P \leq .01$, $^{**}P \leq .001$; d = effect size. *P*-values marked in bold indicate numbers that are significant on the 95% confidence limit.
[a]Pediatric brain tumor survivors versus normative group.

Associations Between Impairments in Functioning and Fatigue, with Participation

In PBTS with limited participation the majority of impairments in cognitive, psychological, physical, and sensory functioning (median CAFI score: 54.9 vs 39.2; $P \leq .01$) were significantly more frequently reported compared to PBTS with age-expected participation. Only speech, vision, and hearing problems as well as physical symptoms (ie headaches, dizziness, and nausea) were not associated with limited participation ($P \geq .13$). (Supplementary Table 5).

In PBTS with limited participation, parents reported more fatigue on all scales: general fatigue, sleep/rest fatigue, and cognitive fatigue, compared to children with age-expected participation ($P \leq 0.03$). In addition, children with limited participation themselves reported more general fatigue and cognitive fatigue ($P \leq .01$) than children with age-expected participation (Supplementary Table 5).

Furthermore, PBTS with age-expected participation ($n = 38$) had similar levels of general, sleep/rest, and cognitive fatigue compared to normative values of Dutch children ($P \geq .32$).

Discussion

Curation from a pediatric brain tumor requires very intensive treatment. After treatment, survivors can be left with a brain injury that predisposes them to several limitations, challenging their ability to participate in daily life.

In this cross-sectional study of 91 PBTS, which is the first with a substantial percentage of younger children (ie 57% aged 4–12 years), we found that in more than half of these children limitations in participation at home, in school, and in community life situations were reported. This frequency was lower compared to the 72% in a previous study in 345 Dutch children and young adults (5–24 years) with acquired brain injury using the same cutoff point (CASP < 97.5).[22] However, as their cohort consisted exclusively of patients who received treatment at a rehabilitation center this would indicate that they all had impairments. Also, the majority (74%) were patients with traumatic acquired brain injury, making an adequate comparison with our cohort difficult. In contrast, the results from another study in 112 Dutch children and young adults (6–22 years)[27] showed limited participation – measured with CASP – in 42% of participants with acquired brain injury 2 years after onset, which is less than in our study. Again, comparison is difficult as 77% of their cohort patients had a traumatic brain injury and not all of the remaining 23% were PBTS.

Our results show that impairments in functioning (ie cognitive, physical, psychological, and sensory) are frequently experienced as problems – minor or major – in PBTS. We found that younger age at diagnosis (<6 years) was associated with more impairments in functioning, which is in accordance with previous studies in PBTS where younger age at treatment has been related to more disability.[3,28]

Active surveillance was the only factor that was positively associated with participation limitations, which is not very surprising because these children did not need treatment in view of their tumor type, location, or lack of tumor

progression. They would have had adequate functioning and stable neurology. We did not find any other patient, tumor- or treatment-related factors influencing participation. Previous studies among PBTS with a comparable follow-up time (1–15 years) did report that recurrent neurosurgery, shunt revisions, and chemotherapy were associated with major disabilities and poorer motor skills.[3,15,28] We found these factors to be associated with fatigue in our cohort but not with participation or impairments in functioning. A potential explanation is the heterogeneity of our cohort with various types of brain tumors and/or overlap between treatment modalities, which challenges detecting relationships.

We did find that general and cognitive fatigue were important factors associated with participation ability. Especially striking was that PBTS with age-expected participation not only had less fatigue than the children with limited participation, but also that their fatigue levels were no different from the normative values of Dutch children. This may indicate that fatigue is an important factor in the ability for PBTS to participate.

Fatigue was assessed using a validated instrument with normative values of children from the general Dutch population. It is one of the first studies where this instrument was used in PBTS <12 years of age.

Parents and children both reported increased fatigue when a procedure for treatment of hydrocephalus (such as an endoscopic third ventriculostomy or ventriculoperitoneal shunt placement) had taken place compared to children who did not have hydrocephalus, which may be due to the severity of this often acute complication rather than the procedure itself. However, it was uncertain whether it was the presence of preoperative hydrocephalus, the attendant difficulties at surgery, or the actual need for a postoperative shunt following tumor resection, that posed the risk.[6]

In our cohort PBTS with NF-1 reported increased general fatigue compared to those without NF-1, which was expected because children with NF-1 reported more perceived fatigue.[29]

We expected to find an association between children who received radiotherapy and fatigue since radiotherapy is a known risk factor for decreased processing speed and cognitive decline,[6] which has been associated with more cognitive fatigue in PBTS.[30] The reasons we did not find such an association could be that, first, the number of children in this cohort who had radiation was too small (n = 37, 33%). Second, the large heterogeneity in our cohort makes it difficult to detect such a possible effect in univariable analyses, and we had insufficient power to explore this in multivariable analyses. Third, we did not have exact data on the amount of radiation exposure but could only analyze radiotherapy dichotomously, which lowers the chance of finding specific associations.

We expected that longer time since end of treatment would result in better participation and less fatigue. However, we found that the extent of participation limitations, impairments in functioning and fatigue was similar in children <3 and ≥3 years since cessation of treatment. Moreover, when we analyzed time since diagnosis (which differs from time since last treatment because of variations in therapy duration), we found an increase in impairments in functioning and cognitive fatigue in children ≥5 years compared to those <5 years since diagnosis of the brain tumor (P ≤0.04). This raises concerns about whether impairments actually lessen over time. Specific limitations (ie cognitive fatigue) may become more noticeable as the child ages, that is that the phenomenon "growing into deficit" emerges.[15] This phenomenon is based on the assumption that while growing older a child's impairments become more pronounced compared to his peers as the demands of the environment increase.[31,32]

To our knowledge, this is the first study examining participation limitations and fatigue in a relatively large group of children of four years and older after treatment for a brain tumor. Given the acceptable response rate (55%) and that responders did not differ from nonresponders with regard to the majority of characteristics, the results may be considered representative. However, the cohort included a relatively large number of survivors of low-grade tumors. It is conceivable that these children are more likely to be survivors. Nevertheless, children with high-grade tumors known to have good survival rates (eg medulloblastoma) were underrepresented. The reported limitations in this study may therefore be an underestimation, because children with high-grade tumors are expected to experience physical impairments more often due to the location of their tumor (most commonly in the cerebellum).

Furthermore, the following limitations should be taken into account when interpreting the results. First, although the CFFS questionnaire is presented as a promising instrument for children with acquired brain injury,[33,34] so far only one study evaluated psychometric qualities in a relatively small Dutch cohort.[20] Second, although in accordance with previous Dutch studies in children with acquired brain injury,[22,23] the cutoff point of limited participation (CASP < 97.5) we used remains arbitrary. A study using the German CASP version showed a ceiling effect in a disability-free sample (n = 215, 3–11 years) where >50% had a CASP score of 100 (mean: 98),[33] which would support our choice. Third, we were not able to perform multivariable analyses because of high heterogeneity in the cohort and lack of power due to limited sample size, leading to wide confidence intervals. Fourth, due to the design of the study information regarding specific learning difficulties, epilepsy, physical disabilities (eg hemiplegia, cerebellar syndrome), somatosensory, endocrine disorders, and socioeconomic status were not available, but are likely contributory factors of participation ability. Future studies addressing these factors would increase our risk understanding for limited participation.

The results of this study show that participation in PBTS is often reduced and that impairments in cognitive and physical functioning as well as increased fatigue, were negatively associated with participation ability. Participation limitations, impairments in functioning and fatigue appeared did not differ between the short and long term. These results underline the importance of follow-up of children after brain tumor treatment, and their reintegration in daily life.

Fatigue appears a commonly observed issue and yet few recognized interventions seem to be offered or available, despite research showing that in the longer term the levels of fatigue in PBTS remain unsatisfactory. We hypothesize that by recognizing and addressing the problems of fatigue

Table 4. Associations Between Patient, Tumor- and Treatment-related Factors and Parent- and Self-reported Fatigue in PBTS

Determinant	PedsQL-MFS Parent-form								PedsQL-MFS Child-form							
	Total fatigue	*P*	General fatigue	*P*	Sleep/rest fatigue	*P*	Cognitive fatigue	*P*	Total fatigue	*P*	General fatigue	*P*	Sleep/rest fatigue	*P*	Cognitive fatigue	*P*
Age at study time		.73		.36		.99		.91		.30		.41		.69		.22
<11 years (*n* = 44)	67.1 (20)		62.9 (24)		78.5 (17)		59.1 (28)		77.8 (17) 71.6 (19)		70 (20)		72.4 (17)		58.9 (24)	
≥11 years (*n* = 47)	68.7 (21)		67.7 (24)		78.5 (21)		59.8 (28)				74.6 (21)		74.3 (19)		67 (26)	
Age at diagnosis		.18		.14		.83		.09		.24		.7		.5		**.04**
<6 years (*n* = 46)	65 (20)		61.7 (23)		78.1 (18)		54.6 (30)		66.6 (17)		71.7 (18)		71.7 (17)		56 (25)	
≥6 years (*n* = 45)	71 (21)		69.3 (25)		79 (20)		64.7 (25)		72.2 (19)		73.9 (22)		74.9 (19)		69.4 (24)	
Time since diagnosis		.07		.14		.51		**.02**		.34		.74		.62		.07
<5 years (*n* = 53)	71.3 (20)		68.6 (24)		79.9 (19)		65.7 (25)		72.2 (19)		73.9 (22)		74.8 (21)		69.6 (23)	
≥5 years (*n* = 38)	63.2 (20)		60.9 (24)		76.9 (18)		51.1 (30)		67.8 (17)		72.1 (19)		72.5 (16)		58.3 (26)	
Sex		.38		.49		.27		.67		.85		.61		.99		.78
Boy (*n* = 49)	66.1 (22)		63.7 (25)		76.4 (20)		58.2 (31)		70.5 (20)		74.4 (24)		73.6 (20)		65.1 (26)	
Girl (*n* = 42)	70 (18)		67.3 (23)		80.9 (17)		60.8 (26)		69.7 (16)		71.7 (17)		73.7 (17)		63.3 (25)	
Tumor grade[a]		.69		.57		.84		.64		.99		.99		.39		.46
High-grade (*n* = 18)	65.8 (18)		61.9 (25)		79.5 (22)		56.1 (24)		70.1 (19)		73.1 (24)		78 (21)		59.1 (20)	
Low-grade (*n* = 73)	68.3 (21)		66 (24)		78.3 (19)		60.1 (29)		70.1 (18)		73.1 (20)		72.7 (18)		65.3 (26)	
Tumor location		.39		.58		.45		.31		.83		.54		.90		.57
Infratentorial (*n* = 45)	65.9 (19)		63.8 (23)		76.9 (17)		56.3 (28)		70.6 (18)		74.9 (17)		73.9 (17)		62.4 (27)	
Supratentorial (*n* = 46)	69.8 (22)		66.7 (26)		80 (21)		62.5 (29)		69.7 (19)		71.6 (23)		73.4 (20)		65.9 (24)	
Neurosurgery																
Radical or partial resection		.09		.73		.19		**.02**		.56		.77		.56		.09
Yes (*n* = 65)	65.6 (21)		64.8 (24)		76.8 (20)		55.1 (29)		69.4 (18)		73.5 (20)		72.9 (19)		61.3 (25)	
No (*n* = 26)	74.2 (17)		66.9 (24)		82.8 (15)		70.7 (24)		72.6 (18)		71.7 (24)		76.2 (17)		73.9 (24)	
Procedure for treatment of hydrocephalus[b]		**.03**		**.02**		**.02**		.33		**.04**		**.04**		.12		.09
Yes (*n* = 13)	56.1 (23)		50 (22)		66.3 (26)		52.1 (30)		58.5 (20)		59.7 (25)		64.8 (24)		50.9 (18)	
No (*n* = 78)	69.8 (20)		67.9 (24)		80.5 (17)		60.6 (28)		72.1 (17)		75.3 (19)		75.1 (17)		66.4 (26)	
Chemotherapy		.43		.25		.82		.43		.13		.09		.88		**.04**
Yes (*n* = 28)	64.9 (18)		60.2 (23)		77.7 (22)		55.4 (25)		64.2 (19)		65.6 (27)		73 (21)		53.9 (20)	
No (*n* = 63)	68.9 (21)		67.1 (24)		78.8 (18)		60.9 (29)		72.2 (18)		75.6 (18)		73.9 (18)		67.9 (26)	
Cranial radiotherapy		.38		.44		.55		.33		.30		.33		.37		.66
Yes (*n* = 37)	70.4 (20)		68 (24)		80.1 (20)		63.3 (26)		72.9 (17)		76.1 (19)		76.1 (19)		65.9 (23)	
No (*n* = 54)	66.4 (21)		63.8 (24)		77.6 (18)		57.2 (29)		68.1 (19)		71 (22)		71.9 (18)		63.1 (27)	
Active surveillance		.08		.19		.18		.07		.41		.11		.79		.15
Yes (*n* = 8)	79.9 (18)		76 (23)		87 (13)		76.7 (23)		80.6 (18)		91.7 (11)		77.1 (9)		84.7 (26)	
No (*n* = 83)	66.7 (20)		64.2 (24)		77.6 (19)		57.7 (28)		69.8 (18)		72.1 (21)		73.5 (19)		63.2 (25)	
Neurofibromatosis-1		.65		.14		.80		.91		.12		**.02**		.56		.31
Yes (*n* = 13)	65.4 (18)		55.9 (23)		77.2 (20)		60.3 (24)		59.3 (21)		54.2 (29)		69.4 (19)		54.2 (26)	
No (*n* = 78)	68.3 (21)		66.9 (24)		78.7 (19)		59.3 (29)		71.3 (18)		75.1 (19)		74.1 (19)		65.3 (25)	

Abbreviations: PBTS, Pediatric brain tumor survivors; PedsQL-MFS, Pediatric Quality of Life Inventory – Multidimensional Fatigue Scale.
Results are reported as mean with standard deviation, higher scores indicate less fatigue; *P*-values are based on two-sample *t*-tests. *P*-values marked in bold indicate numbers that are significant on the 95% confidence limit.
[a]Grade I/II indicates low-grade, grade III/IV indicates high-grade.
[b]Endoscopic third *ventriculostomy or ventriculoperitoneal shunt placement.*

in an earlier phase combined with offering structured interventions, may mitigate these problems.

In adult cancer survivors, interventions targeting physical training and psychosocial interventions (such as cognitive behavior therapy) have shown to be effective in the management of cancer-related fatigue.[35–41] Unfortunately, studies on effectiveness of such interventions in pediatric cancer patients are sparse. It has been shown that physical exercise training in childhood cancer patients is feasible, safe, and effective in improving outcomes such as mobility and muscle strength,[42,43] and also that more physically active patients report less fatigue.[44] However, there are no trials that evaluate the effect of physical exercise training on fatigue. To our knowledge, there has been only one noncontrolled pilot study in childhood cancer survivors ($n = 25$, 3 of whom were PBTS), in which a clinically reduction in fatigue following cognitive behavior therapy was found.[45]

Possible underlying phenomena in PBTS will need to be further investigated and should receive special attention in health care and in multidisciplinary follow-up.

Supplementary Data

Supplementary data are available at *Neuro-Oncology Advances* online.

Keywords

fatigue | impairments | participation | pediatric brain tumor survivors

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