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Title: Associations between Adult Primary Brain Tumor Survivors' Behavioral Executive Functions, Health Related Quality of Life and their Caregivers' Health Related Quality : A cross-sectional study

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Ethics approval

The present study received French regulatory ethical approval (Comité de Protection des Personnes Ouest II, n°2015/27, ID-RCB n°2015-A01192-47) which includes the International Review Board Authorization (N°NCT02693405).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

Participants signed informed consent regarding publishing their data.

Conflicts of interest

The authors have no conflict of interest to declare.

Authors' contribution

JB, PA and DLG contributed to the study conception and design. PM, VR, RS and MD recruited participants. Material preparation, data collection and analysis were performed by NC, AR and JB. JB supervised the project. NC and JB wrote the first version of the manuscript. All authors commented on the manuscript.

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ABSTRACT

Objective: The present study focused on adult primary brain tumor (PBT) survivors' caregivers. The main objective was to study associations between PBT survivors' health related quality of life (HRQOL), their behavioral executive functions (EF) and their caregivers' HRQOL.

Methods: Forty PBT survivors of PBT and 37 caregivers (mostly patient's spouses 81.08%; $n= 30$) participated in the study. PBT survivors completed a cancer related Quality of Life (QOL) questionnaire. Caregivers completed informant rated HRQOL and behavioral EF reports relating to PBT survivors and a self-rated HRQOL questionnaire relating to themselves. Correlational and multiple regression analyses were conducted.

Results: No associations were found between caregivers' physical HRQOL and PBT survivors' HRQOL nor behavioral EF. Analyses yielded several significant correlations between caregivers' mental HRQOL and variables pertaining to PBT survivors' HRQOL and behavioral EF. Multiple regression analyses showed that caregivers' mental HRQOL is predicted by PBT survivors' mental HRQOL, global cancer related QOL scores and global behavioral EF scores.

Conclusions: This study provides evidence suggesting that during the survivorship phase, at an average of 3.67 (SD=2.31) years following treatment for a PBT, caregivers mental HRQOL is linked to PBT survivors' long-term effects. These findings shed some light regarding post-cancer care for both survivors and their caregivers.

INTRODUCTION

Given improvements in survival rates, primary brain tumor (PBT) survivor's longevity has increased. Yet, such progress in survival rates is accompanied by the long-term consequences of cancer and its treatments. These physical, psychosocial, emotional or cognitive consequences induce health-related quality of life (HRQOL) impairments. Indeed, adult PBT survivors' HRQOL impairments have been highlighted by previous studies [1-3]. When compared to survivors from other cancers, PBT survivors seem to suffer from stronger consequences regarding their autonomy [4].

In addition, a cancer diagnosis has a significant impact upon patients' family members [5]. The disease's impact upon HRQOL does not only affect patients, but their primary caregivers as well. For instance, in a study comprising several cancer types [6], results showed that brain cancer patients' caregivers were amongst those reporting lowest HRQOL scores. Indeed, as highlighted by Sherwood et al. [7], PBT caregivers care for someone who suffer concomitantly from an oncological disease as well as neurological and neuropsychiatric sequelae. For example, adult glioma patients' caregivers set up a specific subset of caregivers as they are particularly exposed to patients' mental and physical disorders [8-9]. Another study showed that caregivers of patients suffering from highly malignant central nervous system tumor in the acute phase, are at greater risk of HRQOL impairments when compared to caregivers of patients with systemic tumors not involving the central nervous system and having a comparable life expectancy [10].

As stressed by Sherwood, Cwiklik and Donovan [11], PBT patients' caregivers have not received much interest in the research literature (*e.g.*, these authors identified 36 descriptive studies and six intervention studies in their review). Moreover, research conducted upon caregivers in oncology settings, tends to focus on the active treatment phase or the end of life stage. Yet caregiver's roles change while transitioning from the care trajectory into the

survivorship phase [12]. For instance, a previous study [13] demonstrated that certain functional dimensions, as well as the total score of cancer patients' HRQOL were associated with each dimension of their caregivers' QOL (all dimensions and total scores). Furthermore, results from another study focusing on PBT patients during the active treatment phase [14], highlighted that caregivers' HRQOL was more compromised than that of PBT patients. Yet, the same study failed to demonstrate correlations between patients' clinical and psychological variables and their caregivers' wellbeing (HRQOL, Anxiety, Depression and Caregiver burden). To our knowledge, previous studies have not focused on analyzing the associations between adult PBT survivors' HRQOL and their caregivers' HRQOL specifically during the survivorship phase.

Research on PBT survivors has concluded that long-term adverse effects can follow [15-16]. These include medical, physical, psychosocial and cognitive sequelae. Even if few studies are devoted to late cognitive effects in adult PBT survivors, these have identified impairments in cognitive functions including attention, language, memory and executive functions (EF) [17]. EF are defined as high-level cognitive processes assumed to underlie behavioral adaptation and regulation in daily life [18]. Studies conducted among adult PBT patients in the active treatment phase [19-20], have stressed PBT patients' executive limitations thorough self-reports, thus demonstrating that these difficulties may negatively impact the resumption of daily life activities. Specifically, a recent study conducted among adult PBT survivors (inclusion criteria : at least two years following the end of treatments) provided evidence suggesting that at an average of 3.67 years following treatment for a PBT, behavioral EF difficulties are reported by both patients and their caregivers [21].

The present study focused on PBT survivors' caregivers' HRQOL. The following research questions were addressed: (1) Is HRQOL in adult PBT survivors associated to their caregivers' HRQOL? (2) Are PBT survivors' behavioral EF linked to their caregivers'

HRQOL? Regarding the first question, we hypothesized that, as shown by previous studies concerning cancer patients [13], caregivers' HRQOL would be linked to PBT survivors' HRQOL. The present study specifically addresses this issue during the survivorship phase, to our knowledge previous studies have not addressed this issue in this stage of PBT patients' care trajectory. Moreover, since previous studies suggest that PBT patients' cognitive difficulties that alter normal functioning (e.g., executive, attention and memory deficits) are linked to PBT patients' HRQOL [21] and might increase caregivers' distress [22], we hypothesized that in the case of PBT survivors' caregivers, late behavioral EF effects would be associated to caregivers' HRQOL. Most studies assessing PBT patients' EF and its associations to HRQOL focus on performance-based tasks (e.g., [23]), yet the present study is based upon informant reports regarding PBT survivors' executive difficulties when carrying out daily life activities.

METHODS

Following French regulatory ethical approval (Comité de Protection des Personnes Ouest II, n°2015/27, ID-RCB n°2015-A01192-47) which includes the International Review Board Authorization (N°NCT02693405), data were collected between June 2016 and December 2018.

Design, participants and recruitment

The present study has a cross-sectional design. Each participant (PBT survivors and caregivers) signed an informed consent regarding their enrollment and future publishing of their anonymous data.

After verifying eligibility criteria, 40 PBT survivors were recruited among neurosurgery departments in three university hospitals located in northwestern France. Inclusion criteria were as follows: (1) patients had to be aged between 20 and 59 years to

avoid the effect of normal aging on neurocognitive functioning; (2) they must have been treated (chemotherapy, radiation therapy or surgery) for a PBT. Patients with brain metastases of non-central nervous system tumors were not included. (3) As this study is devoted to functional late effects of PBT, patients should have completed their treatment at least two years prior to enrollment in the study. In addition, since the study's methodology (self-reports) requires a satisfactory level of understanding, (4) patients should not have presented major cognitive/understanding impairments, and (5) they had to be French native speakers. Medical data (tumor type and location, type of treatment, time since end of treatments) were collected.

After enrollment, within the hospital's premises and in a quiet room, PBT survivors completed the QLQ-C30 BN20 self-reports as well as a questionnaire gathering socio-demographic data (age, sex, educational level, professional status and laterality). Before they returned to their homes, the informant version of the SF-36 and the BRIEF-A was given to patients who were asked to transmit it to a caregiver (e.g., family member, spouse). The self-reported SF-36 concerning caregivers' HRQOL was also handed to them. A few days later, one of the study's investigators called the caregiver to ask if he/she had any questions concerning the informant reports (SF-36 and BRIEF-A) as well as the self-reported SF-36 concerning their own HRQOL. This also ensured that he/she had effectively completed the questionnaire. Caregivers' were asked to mail back questionnaires to the study's investigator after completion. No exclusion criteria were considered in the recruitment of caregivers.

Measures

Behavioral EF was evaluated through the informant-rated French version of the Behavior Rating Inventory of Executive Functioning-Adult version (BRIEF-A; [24]). The questionnaire comprises 75 items that assess the frequency of different aspects of patients' EF-related problems. A Global Executive Composite (GEC) can be obtained and broken

down into two index scores: (1) the Behavioral Regulation Index (BRI) includes four subscales (Inhibition, Shift, Emotional Control and Self-Monitor) and (2) the Metacognition Index (MCI) consists of five subscales (Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials). Raw scores are summed onto respective subscale and index scores and consequently transformed to age- and gender-normalized T-scores (Roy et al., 2015). Higher scores designate higher deficits.

PBT survivors' HRQOL was evaluated through the French version of the Medical Outcomes Study Short Form (SF-36) informant-rated questionnaire [25]. This instrument is proven to be valid and reliable in brain tumor patients [26]. It measures individuals' generic health status through eight dimensions [physical and social functioning, role limitations (physical and emotional problems), bodily pain, general health, mental health, vitality [25]. Two composite scores can be calculated for a physical component score (PCS) and a mental component score (MCS). Higher scores reflect higher levels of functioning and better health status. All subscales presented good internal consistency.

A specific cancer related Quality of Life (QOL) questionnaire (self-rated) was also administered to PBT survivors: the EORTC QLQ-C30 [27]. For the purposes of this study, the questionnaire's five functioning scales (physical functioning, social functioning, role functioning, emotional functioning, and cognitive functioning) and the scale for global QOL were used. All scales were scored according to EORTC guidelines, resulting in scores ranging from 0 to 100 points. PBT survivors completed the French version of these questionnaires [28]. Higher scores for a functional scale represent a healthy level of functioning and higher scores for the global health status represent high HRQOL.

Finally, caregivers' HRQOL was evaluated through the French version of the Medical Outcomes Study Short Form (SF-36) self-rated questionnaire [26]. It measures individuals' generic health status through eight dimensions [physical and social functioning, role

limitations (physical and emotional problems), bodily pain, general health, mental health, vitality]. Two composite scores can be calculated for a physical component score (PCS) and a mental component score (MCS). Higher scores reflect higher levels of functioning and better health status.

Statistical Analyses

Raw data were analyzed using STATISTICA Version 13.3 software (Tibco Software Inc, Palo Alto, CA, USA). First, Pearson product-moment correlations were used to study the relationships between PBT survivors' behavioral EF (informant reported BRIEF-A), PBT survivors' HRQOL (informant reported SF-36 and self-reported QLQ- C30-BN20) and caregivers' HRQOL (self-reported SF-36). Second, multiple regression analyses were then conducted to examine the predictive value of PBT survivors' behavioral EF and HRQOL variables for caregivers' HRQOL. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

Sample characteristics

Patients' sociodemographic characteristics and illness information is presented on Table 1. As to caregivers ($N = 37$), they were mostly patient's spouses (81.08%; $n = 30$) or a close family member living with the patient (18.92%; $n = 7$). Some informant report data was lost since three patients' caregivers did not return their questionnaires by mail. Therefore, statistical analyses were conducted for 40 PBT patients' self-reports (QLQ-C30 and QLQ-C20), 37 caregivers' informant reports (informant reported SF-36) and 37 caregivers' self-reports (SF-36).

INSERT TABLE 1 ABOUT HERE

Correlational Analyses

Pearson correlations were conducted to test associations between caregivers' HRQOL (SF-36 PCS and MCS scores) and patients' HRQOL scores (SF-36 PCS and MCS scores and QLQ-C30 scores). No significant correlations were found between caregivers' SF-36 PCS scores and patients' HRQOL scores. Several significant correlations were found between caregivers' SF-36 MCS scores and patients' HRQOL scores: (1) Patients' SF-36 MCS ($r = 0.40$; $p \leq 0.05$), (2) QLQ-C30 Global QOL ($r = 0.42$; $p \leq 0.01$) and (3) QLQ-C30 Cognitive Functioning ($r = 0.42$; $p \leq 0.01$).

Moreover, Pearson correlations were conducted to test associations between caregivers' HRQOL (SF-36 PCS and MCS scores) and patients' behavioral EF scores (BRIEF-A informant reports). No significant correlations were found between caregivers' SF-36 PCS scores and patients' behavioral EF scores. Several correlations were found between caregivers' SF-36 MCS scores and patients' BRIEF-A informant reports: (1) Initiate ($r = -0.34$; $p \leq 0.05$), (2) Working Memory ($r = -0.39$; $p \leq 0.05$), (3) Plan/Organize ($r = -0.37$; $p \leq 0.05$), (4) Task Monitor ($r = -0.50$; $p \leq 0.01$), (5) Metacognition Index ($r = -0.40$; $p \leq 0.05$) and (6) Global Executive Composite ($r = -0.40$; $p \leq 0.05$).

INSERT TABLE 2 ABOUT HERE

Multiple Regression Analyses

A multiple regression analysis was conducted to examine the predictive value of patients' SF-36 MCS for caregivers' HRQOL (SF-36 MCS scores). Patients' MCS scores were considered as the independent variable in the prediction of caregivers' SF-36 MCS scores. This score accounted for 15.82% ($p=.02$) of the variance in caregivers' SF-36 self-rated MCS scores ($F = 5.64$; $df=1, 30$).

A second multiple regression analysis was conducted to examine the predictive value of patients' QLQ-C30 Global QOL scores for caregivers' HRQOL (SF-36 MCS scores).

Patients' QLQ-C30 Global QOL scores were considered as the independent variable in the prediction of caregivers' SF-36 MCS scores. This score accounted for 17.62% ($p=.01$) of the variance in caregivers' SF-36 self-rated MCS scores ($F = 7.06$; $df=1, 33$).

Finally, a third multiple regression analysis was conducted to examine the predictive value of behavioral EF variables (BRIEF-A) for caregivers' HRQOL (SF-36 MCS scores). Given the significant number of correlations between BRIEF-A subscales and caregivers' MCS scores, only GEC scores were considered to simplify analyses and reduce redundancy. BRIEF-A GEC scores were considered as the independent variable in the prediction of caregivers' SF-36 MCS scores. This score accounted for 12.60% ($p=.04$) of the variance in caregivers' SF-36 self-rated MCS scores ($F = 4.76.10$; $df=1, 33$).

DISCUSSION

The present study, focused on adult PBT survivors' HRQOL and behavioral EF, and their associations with caregivers' HRQOL. Is HRQOL in adult PBT survivors associated to their caregivers' HRQOL? Are PBT survivors' behavioral EF linked to their caregivers' HRQOL? To our knowledge, this is the first study aiming to answer these questions during the PBT survivorship phase.

Our first hypothesis was that caregivers' HRQOL would be linked to PBT survivors' HRQOL. Results partially validated this hypothesis given that several aspects patients' HRQOL (MCS, global QLQ score, Cognitive Functioning QOL domain) were positive correlated to caregivers' MCS (mental health component of HRQOL). Yet no associations were found between PBT survivors' HRQOL caregivers' PCS scores (Physical health component of HRQOL). Furthermore, results confirmed the predictive value of PBT survivors' MCS and global cancer related quality of life (QLQ-C30 global QOL score) upon their caregivers' mental HRQOL (SF-36 MCS).

Our second hypothesis was that PBT survivors' behavioral EF effects would be associated to caregiver's HRQOL. Even if no associations were found between PBT survivors' behavioral EF and their caregivers' physical HRQOL (PCS scores), results concerning caregivers' mental HRQOL (SF-36 MCS) strongly support this hypothesis. Indeed, several dimensions of PBT survivors' daily EF (ability to begin an activity, working memory, ability to anticipate future events, ability to put order in work and ability to monitor success and failure in problem solving) were linked to their caregivers' mental HRQOL. Moreover, PBT survivors' overall daily EF (Global Executive Composite summary score) was a predictor of caregivers' mental HRQOL.

As brought forth by previous studies, PBT patients' caregivers, represent a subset of caregivers particularly exposed to mental and physical disorders [8-9]. Our findings shed some light regarding the specificities of caregiving for a PBT survivor: caring for someone presenting executive dysfunctions during their daily lives. Even if we did not focus on caregiver burden (*e.g.*, [14]), our results suggest that PBT survivors' behavioral executive needs fuel their caregivers' distress.

Our findings clearly highlight that caregivers' mental HRQOL is impacted when caring for a PBT patient during the survivorship phase. As stressed by Kim and Given [29], the quality of life (QOL) of family caregivers of individuals with cancer varies along the illness trajectory. Thus, our results highlight the importance of assessing the ongoing adjustment caregivers over time, beyond the time of diagnosis and treatment. As demonstrated by previous studies [30], stress and burden in PBT caregivers seems to unfold over the course of a year after diagnosis, stressing that early intervention programs could ensure low initial levels of burden. On the same vein, our results pertaining to caregivers mental HRQOL during the survivorship phase, support intervention programs in the post-treatment phase which might prevent caregiver distress

It is important to recognize some of the present study's limitations, which could be addressed by future research. The first limitation regards the measurement of PBT survivors' HRQOL. Since the present study focused on the survivorship phase, generic measures such as SF-36 [26] or cancer specific HRQOL measures like QLQ-C30 [27] might be relevant within the active treatment phase and less sensitive during the survivorship phase [31] when assessing PBT survivors' HRQOL. A similar limitation concerns the evaluation of caregivers' HRQOL. We chose a generic questionnaire, which is the most widely used when studying HRQOL. Yet, a specific measure evaluating the impact of caregiving on QOL within the oncological setting (e.g., [32]) could have been employed. Moreover, our study lacks measurements regarding caregivers' psychological variables such as caregiver burden, anxiety and depression, perceived stress level or fear of cancer recurrence as assessed in a recent study [33] revealing that this emotional variable is an important determinant of caregiver distress in the case of PBT.

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Table 1. Patients' socio-demographic characteristics and patients' illness information

Characteristic	PBT Patients (n= 40)
	Mean (\pm SD) / Number (%)
Age (Years)	41.20 (11.06)
Gender	
Men	28 (70%)
Women	12 (30%)
Laterality	
Left handed	5 (12.5%)
Right handed	34 (85%)
Ambidextrous	1 (2.5%)
Bilingual	4 (10%)
Visual aid (glasses)	25 (62.5%)
Education (Years)*	11.83 (3.29)
End of treatments (Years)	3.67 (2.31)
Tumor Diagnosis	
Oligodendroglioma	11 (27.5%)
Oligoastrocytoma	5 (12.5%)
Astrocytoma	6 (15%)
Glioblastoma	3 (7.5%)
Glioma	5 (12.5%)
Other tumors**	10 (25%)
Treatments	
Chemotherapy	20 (50%)
Radiotherapy	20 (50%)
Tumor Resection	39 (97.5%)
Chemotherapy & Radiotherapy	16 (40%)
Chemotherapy & Tumor Resection	19 (47.5%)
Radiotherapy & Tumor Resection	18 (45%)
Chemotherapy & Radiotherapy & Tumor Resection	15 (37.5%)
Epileptic Seizures	
No	37 (92.5%)
Yes	3 (7.5%)

Note. *Number of years after 1st grade (elementary school); **craniopharyngioma, meningioma, medulloblastoma, neurocytoma, germinoma.

Table 2. Pearson correlations – Associations between caregivers' HRQOL scores and patients' behavioral EF scores and patients' HRQOL scores

	Caregivers' SF-36 MCS Scores <i>M</i> = 23.11 (<i>SD</i> = 1.49)	Caregivers' SF-36 PCS Scores <i>M</i> = 29.49 (<i>SD</i> = 0.70)
BRIEF-A Inhibition	-0.13	0
<i>M</i> = 47.81 (<i>SD</i> = 7.87)	<i>NS</i>	<i>NS</i>
BRIEF-A Shift	-0.31	-0.02
<i>M</i> = 48.37 (<i>SD</i> = 9.80)	<i>NS</i>	<i>NS</i>
BRIEF-A Emotional Control	-0.01	0.01
<i>M</i> = 50.19 (<i>SD</i> = 10.15)	<i>NS</i>	<i>NS</i>
BRIEF-A Self-Monitor	-0.06	0.02
<i>M</i> = 49.24 (<i>SD</i> = 10.77)	<i>NS</i>	<i>NS</i>
BRIEF-A Initiate	-0.34	0.01
<i>M</i> = 49.41 (<i>SD</i> = 11.32)	<i>p</i> = .05	<i>NS</i>
BRIEF-A Working Memory	-0.39	-0.06
<i>M</i> = 51.86 (<i>SD</i> = 11.77)	<i>p</i> = .02	<i>NS</i>
BRIEF-A Plan/Organize	-0.37	0
<i>M</i> = 51.16 (<i>SD</i> = 11.71)	<i>p</i> = .03	<i>NS</i>
BRIEF-A Task Monitor	-0.50	-0.15
<i>M</i> = 51.14 (<i>SD</i> = 9.81)	<i>p</i> = .01	<i>NS</i>
BRIEF-A Organization of Materials	-0.18	-0.12
<i>M</i> = 47.70 (<i>SD</i> = 7.35)	<i>NS</i>	<i>NS</i>
BRIEF-A Behavioral Regulation Index (BRI)	-0.17	0
<i>M</i> = 48.73 (<i>SD</i> = 8.84)	<i>NS</i>	<i>NS</i>
BRIEF-A Metacognition Index (MCI)	-0.40	-0.04
<i>M</i> = 50.27 (<i>SD</i> = 9.77)	<i>p</i> = .02	<i>NS</i>
BRIEF-A Global Executive Composite (GEC)	-0.36	-0.04
<i>M</i> = 49.22 (<i>SD</i> = 9.73)	<i>p</i> = .04	<i>NS</i>
Patients' SF-36 MCS	0.40	-0.05
<i>M</i> = 23.12 (<i>SD</i> = 1.13)	<i>p</i> = .02	<i>NS</i>
Patients' SF-36 PCS	0.34	0.27
<i>M</i> = 28.94 (<i>SD</i> = 1.17)	<i>NS</i>	<i>NS</i>
QLQ-C30 Global QOL	0.42	-0.05
<i>M</i> = 76.04 (<i>SD</i> = 17.21)	<i>p</i> = .01	<i>NS</i>
QLQ-C30 Physical Functioning	0.14	-0.03
<i>M</i> = 92.83 (<i>SD</i> = 11.13)	<i>NS</i>	<i>NS</i>
QLQ-C30 Social Functioning	0.10	-0.06
<i>M</i> = 83.75 (<i>SD</i> = 24.89)	<i>NS</i>	<i>NS</i>
QLQ-C30 Role Functioning	0.17	-0.09
<i>M</i> = 91.25 (<i>SD</i> = 15.55)	<i>NS</i>	<i>NS</i>
QLQ-C30 Emotional Functioning	0.03	0.06
<i>M</i> = 74.79 (<i>SD</i> = 21.72)	<i>NS</i>	<i>NS</i>
QLQ-C30 Cognitive Functioning	0.42	0
<i>M</i> = 79.58 (<i>SD</i> = 19.42)	<i>p</i> = .01	<i>NS</i>