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ORIGINAL PAPER

Outcome of children with low-grade cerebellar astrocytoma: long-term complications and quality of life

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Abstract
Objects To study the long-term outcome of surgically treated low-grade cerebellar astrocytomas in children.
Materials and methods We followed 31 consecutive patients under 16 years of age who were diagnosed between 1980 and 2005 in a single institution. In 21 of 31 survivors (median follow-up time 7.9 years; range 5.6–27.4 years) who agreed to participate, tumor control, neurological and cognitive complications, and their impact on behavioral and emotional adjustment and health-related quality of life (HRQoL) were comprehensively assessed qualitatively and quantitatively.
Results Neurological sequelae were found in 43%. However, age-appropriate ability to perform daily life activities was normal in all patients. Remarkably, cognitive deficits leading to significant school problems occurred in 19% and behavioral and emotional adjustment disturbances in 27%. In comparison with healthy controls, the survivors rated their HRQoL similarly or even higher.
Conclusion Childhood low-grade cerebellar astrocytomas have an excellent cure rate by tumor surgery alone. When compared with other pediatric brain tumors, the risk of neurological, cognitive, emotional, and behavioral complications is relatively small. HRQoL is similar to that of healthy controls.

Keywords Brain neoplasm · Child · Astrocytoma · Outcome assessment · Quality of life

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Introduction

Low-grade astrocytomas comprise approximately 30–40% of all primary brain tumors in childhood. For low-grade cerebellar astrocytomas, surgery represents the treatment of choice. Despite their benign biological nature, low-grade cerebellar astrocytomas can cause not only permanent neurological damages such as truncal ataxia, dysmetria, nystagmus, and dysarthria [1, 2] but also behavioral and emotional problems and deficits in several cognitive functions including attention, memory, processing speed, interference, and verbal fluency [1–7]. These cognitive and behavioral impairments represent the cerebellar cognitive affective syndrome initially described by Schmahmann and Sherman [8] in adults and subsequently expanded to the pediatric age. What is not yet sufficiently documented is the impact that such late effects have on the quality of life (QoL) of the survivors [9].

Interest in the measurement of QoL has expanded considerably over the past 10 years, with an increasing understanding of the importance of patients' perspectives [10]. According to the World Health Organization (WHO 1948), health-related quality of life (HRQoL) is seen as a multidimensional concept including physical, social, cognitive, and emotional functioning. The subjective perception and appraisal of functioning are as important as

objective health because individuals with the same objective health status can report very different QoL [11]. For assessing HRQoL in pediatric populations, there is wide agreement that instruments should be multidimensional, sensitive to cognitive development, and easy to complete and should encompass the broadest age range possible. Furthermore, they should meet the required psychometric parameters of sensitivity, reliability, and validity [12–14].

As an extension of our previous studies on outcome in pediatric low-grade cerebellar astrocytomas [1], we followed 31 consecutive patients at a single hospital diagnosed between 1980 and 2005.

Material and methods

Patient selection

Between January 1980 and December 2005, 31 patients below the age of 16 years with cerebellar low-grade astrocytoma were diagnosed at the University Children's Hospital of Zurich, Switzerland. All diagnoses were confirmed by histological assessment of a tumor specimen obtained at surgery. Clinical information on the 31 patients included date of birth, date of diagnosis, therapy received, and follow-up. Gross total resection was defined as complete tumor removal as reported by the operating neurosurgeon and confirmed by postoperative neuroimaging (magnetic resonance imaging or computed tomography). The median age of all patients at diagnosis was 8.1 years (range 2.4–15.5 years). As of October 2007, 30 of the 31 patients were alive. Seven patients could not be contacted because they had moved to another country and three patients refused to participate. To our knowledge, two of these patients had no neurological sequelae, whereas one had mild truncal ataxia and ocular movement disorder. The remaining 21 patients agreed to be interviewed and to be assessed by quantitative measures. Eleven patients were female and ten were male. The median age at diagnosis of the study patients was 7.8 years (range 2.4–14.3 years) and the median age at assessment was 15.8 years (range 8.3–41.0 years). Six patients (patient nos. 4, 7, 9, 11, 12, and 15) were included in an article focused on neuropsychological findings ([1]; patient nos. 3, 4, 5, 13, 14, and 19). Approval to perform the study and to link study data to clinical data was obtained from the Institutional Review Board.

Semistructured interview

After receiving the written informed consent of parents and patients, the questionnaires were posted to the patients and the interview was performed by telephone. Combined with the information obtained from medical notes, the data gathered from the interview were intended to give a descriptive picture of the participant's past and present life situation. Therefore, the interview included questions about the time of diagnosis and treatment, current medication, physical and visual functioning, height and weight, satisfaction with physical appearance, emotional functioning, and interpersonal relationships including school performance, personal interests, social activities, thoughts, family relations, intimate relationships, and wishes about the future ("Appendix"). The questions were phrased in an easily comprehensible way and almost every question had a yes–no answer.

Youth Self-Report, Child Behavior Checklist, and Brief Symptom Inventory

German versions of the Youth Self-Report (YSR) [15, 16] and the Child Behavior Checklist (CBCL) [17, 18] were used to assess behavioral and emotional problems. Details about these instruments have been published in our previous studies on outcome in craniopharyngioma, medulloblastoma, and intraspinal tumors [19–21]. YSR and CBCL were used in the present study for nine patients aged between 12 and 20 years (median age 15.8 years). To assess emotional health in older patients, we used a German version of the 53-item Brief Symptom Inventory (BSI), which includes symptoms over the previous 7 days [22, 23]. The BSI includes three global indices of distress and nine symptom dimensions. Raw scores were converted to *T* scores based on healthy population norms and dichotomized using a cut point of 63. Those with *T* scores >62 were classified as having poor emotional health. BSI was used in the present study for ten patients aged between 15 and 41 years (median age 22.6 years).

Fertigkeitenskala Munster–Heidelberg Abilities Scale

To assess the ability to perform daily life actions, the German Fertigkeitenskala Munster–Heidelberg Abilities Scale (FMH) was used [24]. Details about this instrument have been published in our previous study on outcome in craniopharyngioma [19]. FMH was used in the present study for all patients.

Pediatric Quality of Life Inventory

A German version of the Pediatric Quality of Life Inventory (PedsQL™) was used to measure HRQoL [25, 26]. Details about this questionnaire have been published in our previous studies [19, 20, 27]. In the present study, the PedsQL™ 4.0 Generic Core Scales were used for all patients (n=21). The scores of the study population were compared with the published scores of 401 healthy controls

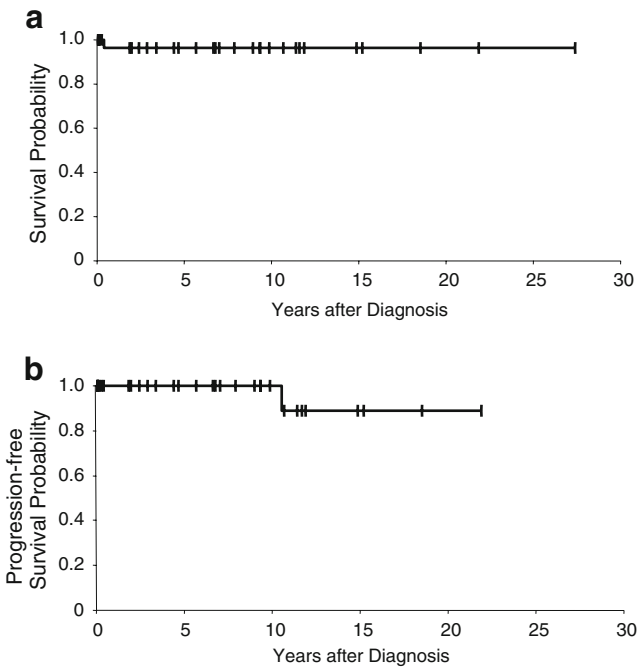

Fig. 1 The Kaplan–Meier curves show the probability of overall survival (**a**) and progression-free survival (**b**) for 31 children with low-grade cerebellar astrocytoma

[28] by single sample *T* tests. Spearman correlation coefficients were calculated to explore the relationship between self-rated and parent-rated PedsQL™ scores and clinical factors. *P* values <0.05 were considered significant.

Results

Local tumor control and relapse-free interval

The median follow-up time of all 31 patients following diagnosis was 6.8 years (range 0.1 to 27.4 years). The 10-year overall survival was 96.2% and the 10-year progression-free survival was 100% as determined by the Kaplan–Meier method (Fig. 1). One patient (diagnosed in the year 1982) died postoperatively with complications due to infection.

For the 21 study patients, median follow-up time was 7.9 years (range 5.6–27.4 years; Table 1). The tumors were located in the cerebellar hemispheres (11 on the right side, eight on the left) and/or midline ($n=10$). Gross total tumor resection was achieved in 19 of 21 patients and incomplete resection in two. In these two patients, the residual tumor was immediately removed. Histology in 20 cases revealed pilocytic astrocytoma WHO I and in one case an astrocytoma WHO II. In all patients, the therapeutic approach consisted of surgery alone. Tumor relapse occurred in one

Table 1 Comparison of FMH scores and PedsQL™ scores with clinical factors of 21 children with cerebellar low-grade astrocytoma

Patient no.	Age at diagnosis (years)	Gender	Tumor location	Tumor resection	VP shunt	Relapse	Tumor reoperation	Follow-up (years)	FMH (centile)	PedsQL™ (self-rated)	PedsQL™ (parent-rated)
1	2.4	Female	R→ML	Total	No	No	No	11.8	25–50	90.22	92.39
2	2.7	Female	L→ML	Total	No	No	No	5.6	50–75	86.96	80.43
3	3.8	Female	L→ML	Subtotal	Yes	No	Yes[a]	6.9	25–50	98.91	98.91
4	4.3	Male	L→ML	Total	No	No	No	18.5	25–50	75.00	
5	4.3	Female	R	Total	No	No	No	21.8	50–75	82.61	
6	5.1	Female	R→ML	Total	No	No	No	6.7	25–50	77.17	70.65
7	5.2	Male	ML	Subtotal	No	No	Yes[a]	10.6	50–75	97.83	82.61
8	5.7	Male	R	Total	No	No	No	4.3	25–50	83.70	83.70
9	5.7	Male	ML	Total	No	No	No	9.8	25–50	98.91	98.91
10	6.7	Female	L→ML	Total	No	No	No	2.8	50–75	91.30	97.83
11	7.8	Male	L→ML	Total	No	No	No	14.8	50–75	77.17	
12	8.1	Male	L→ML	Total	No	No	No	7.8	25–50	97.83	96.74
13	8.1	Male	R	Total	Yes	No	No	2.3	10–25	82.61	81.52
14	9.1	Male	R	Total	No	No	No	3.3	25–50	83.70	71.74
15	9.8	Female	R	Total	No	No	No	15.1	90–95	71.74	
16	11.1	Male	R	Total	No	No	No	1.9	25–50	93.48	92.39
17	11.9	Female	R	Total	No	No	No	9.2	25–50	81.52	
18	12.3	Female	R	Total	No	No	No	4.6	50–75	98.91	97.83
19	13.5	Male	L	Total	No	No	No	6.6	50–75	61.96	94.57
20	13.7	Male	R	Total	Yes	Yes	Yes	27.4	25–50	72.83	
21	14.3	Female	L	Total	No	No	No	11.4	50–75	92.39	

L Left cerebellar hemisphere, *R* right cerebellar hemisphere, *ML* midline
[a] Immediate reoperation because of incomplete primary tumor resection

patient 10.5 years after initial diagnosis (patient no. 20); the recurrent tumor was totally removed surgically. Postoperatively, three patients required the insertion of a ventriculoperitoneal shunt.

Assessment of disabilities and their impact on HRQoL

Together with the information obtained from the medical notes, the data gathered from the patients' physicians, the patients' parents, as well as from the patients themselves served to provide a description of the patients' disabilities and their past and present life situation. Table 2 summarizes this information. Three patients had disorders not related to the cerebellar tumor: one patient (no. 15) with a positive familiar history for epilepsy suffered from photosensitive epilepsy with generalized seizures 7 years after diagnosis. Another patient (no. 21) suffered from back pain after a herniated vertebral disk, and a third patient (no. 1) had a transposition of the great arteries that required cardiac surgery.

Neurological sequelae

Nine of 21 patients (42%) had significant neurological sequelae that persisted during long-term follow-up. These sequelae included limb ataxia (n=8; 38%), truncal ataxia (n=6; 28%), dysarthria (n=1; 5%), and ocular movement disorders (n=1; 5%). Four patients (nos. 2, 11, 13, 16) were having physiotherapy or occupational therapy at the time of follow-up. One patient (no. 10) had speech therapy and two patients (no. 13, 14) had psychological support.

Cognitive function, school performance, and occupation

Seven (33%) of the 21 study patients had difficulties in concentrating (attention deficit). Six patients (28%) described processing speed deficits. Significant school or occupational problems occurred in four (19%) patients: two patients attended a special school, another one had to repeat a school year and the fourth attended a supported workplace.

Physical functioning

Four (19%) of the 21 patients complained about frequent headaches. Two patients (10%) were not satisfied with their physical appearance: the first because of a visible scar on the neck and the second because of a facial asymmetry. All patients confirmed no impairment in physical fitness and none of them used orthotics.

Daily life activities

Twenty (95%) of 21 study patients had FMH scores above the 25th centile indicating normal age-appropriate ability to perform daily life activities. One of the 21 study patients had FMH scores below the 25th centile and none of the scores were below the fifth centile (Table 1).

Table 2 Disabilities and quality of life of 21 long-term survivors with low-grade cerebellar astrocytoma

Characteristics	Affected patients	Limiting quality of life
Neurological functioning		
Limb ataxia	8/21	5/8
Truncal ataxia	6/21	3/6
Dysarthria	1/21	0/1
Ocular movement disorders	1/21	0/1
Paresis	0/21	
Neurocognitive, school and occupation functioning		
Impaired intelligence	4/21	4/4
Attention deficit	7/21	5/7
Processing speed deficit	6/21	5/6
Remedial teaching	4/21	1/4
Impaired choice of occupation[a]	1/8	1/1
Physical functioning		
Frequent headache	4/21	3/4
Not satisfied with physical appearance	3/21	2/3
Impaired fitness	0/21	
Emotional and social functioning		
Behavioral problems	7/21	5/7
Difficulties in making friends	4/21	4/4
No partnership experience[a]	3/8	2/3
Impaired independence[a]	0/8	

[a] Only >19 years of age

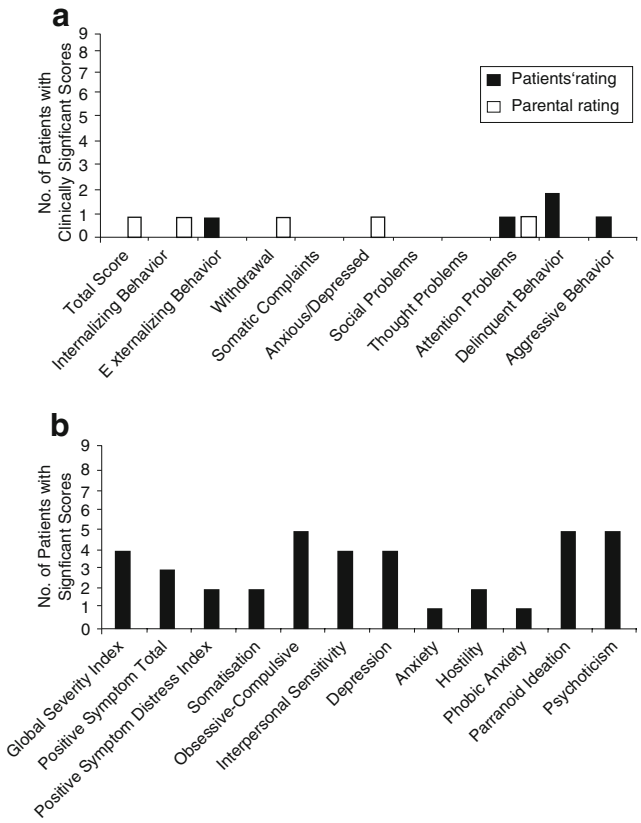

Fig. 2 **a** Behavioral and psychological adjustment problems as rated by the patients with low-grade cerebellar astrocytoma (n=9; Youth Self-Report) and their parents (n=9; Child Behavior Checklist). The numbers of patients with clinically significant scores are shown. **b** Brief Symptom Inventory in survivors of low-grade cerebellar astrocytoma (n=10). The BSI includes three global indices of distress and nine symptom dimensions. Raw scores were converted to T scores based on healthy population norms and dichotomized using a cut point of 63. Those with T scores >62 were classified as having poor emotional health

Behavioral and emotional problems, social life

Based on interviews and clinical records, seven (33%) of the 21 study patients had behavioral problems. Most of them described sadness, anxiety, or general emotional instability. One patient reported aggressive and destructive behavior since diagnosis. In all cases, the symptoms led to unconfident behavior in social live. Four adult patients described difficulties in making friends, which resulted in social isolation. Two females (age 25 years) never had any partnership experience, which was limiting their QoL.

Subjective behavior and emotional problems were assessed by YSR and BSI, dependent on age. Four (26%) of 15 investigated patients had clinically significant total scores. Summarizing the results of both tests, six patients showed significant scores in obsessive or paranoid behavior, four patients in interpersonal sensitivity, anxiety, or depression, four patients in delinquent, hostile, or aggressive behavior, two patients in somatic complaints, and one patient in attention problems. Seven of the 15 patients did not demonstrate clinical significance in any of the subscale scores (Fig. 2).

Based on the parent-rated CBCL, one (11%) of nine survivors had a significant total score. The same patient had a significant score in attention problems. A second patient had significant subscores in internalizing, anxiety–depression, and withdrawal but not a significant total score.

Health-related quality of life

In comparison with healthy controls, the patients with cerebellar astrocytoma rated their HRQoL similar or even better (Fig. 3). Notably, patients with cerebellar astrocytoma rated their physical health higher than did healthy controls (93.01 vs. 84.41; p<0.001). Concordance between patient and parent ratings was relatively good.

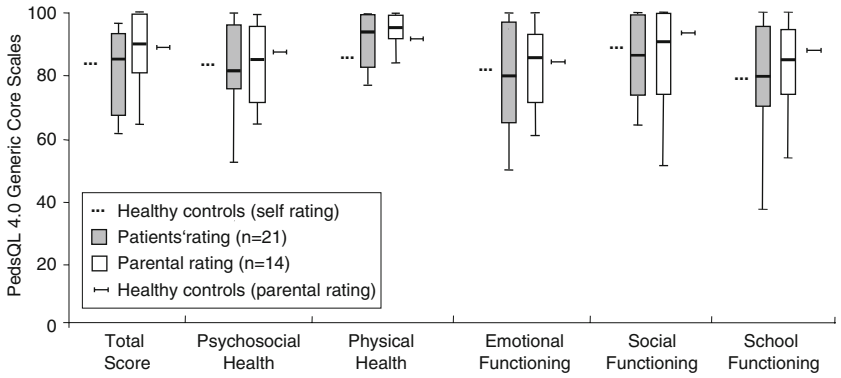

Fig. 3 Health-related quality of life in survivors of low-grade cerebellar astrocytoma rated by the patients and their parents using the PedsQL™ 4.0 Generic Core. *Horizontal lines* are mean values; *solid box* shows 25th to 75th centiles; *whisker bars* represent lowest and highest values. For self-report and parental rating controls, *horizontal lines* are means; there are no boxes or whisker plots because data were not available

Discussion

Low-grade cerebellar astrocytomas are histologically benign tumors with very good tumor control achieved by surgery alone. Ten-year progression-free survival rates range from 81% to 93% [29–31]. In our series, surgery alone was largely successful in disease control. The 10-year progression-free survival was 100% and tumor relapse was observed in only one patient 10.5 years after initial diagnosis. With improved survival rates in pediatric brain tumors, awareness of significant tumor-related and/or therapy-related long-term neurological, cognitive, emotional, or behavioral complications has increased [32–36].

An increasing number of clinical studies has demonstrated cognitive deficits in children with posterior fossa tumors. These long-term problems have been described by Schmahmann and Sherman [8] as "cerebellar cognitive affective syndrome," confirming the importance of the cerebellum for nonmotor functions. The cerebellar cognitive affective syndrome is characterized by problems of executive function, impaired spatial cognition, linguistic difficulties, and personality changes. In two subsequent pediatric series of patients who underwent resection of a cerebellar tumor without additional therapy, Levisohn et al. [4] and Riva and Giorgi [5] described impairments in planning and sequencing, visual–spatial functions, expressive language, verbal memory, and modulation of affect. In a comparable study population, Steinlin et al. reported significant problems for attention, memory, processing speed, and interference. Furthermore, visuoconstrictive abilities and verbal fluency were also affected. Behavioral deficits could be detected in 33% of patients and attention deficits were marked in 12.5% [1]. In a similar study, Aarsen et al. [2, 3] found that approximately 61% of children with low-grade astrocytomas showed impairments in interpersonal relationship, school functions, and behavior. Our study confirms these previous findings concerning neurological and cognitive impairments in long-term survivors of cerebellar tumors. Indeed, in the present study, 43% of the patients showed persistent neurological sequelae including limb and/or truncal ataxia, dysarthria, and ocular movement disorders. Attention and processing speed deficits occurred in 33% and significant school problems in 19%, confirming the abnormalities in neuropsychological subscales described in the literature [1, 4, 5]. When compared with survivors of childhood medulloblastoma and craniopharyngioma [19, 20], these changes were rather discreet: the ability to perform daily life activities was age appropriate in all patients.

Social functioning was rated by the patients and the parents as seldom impaired. Only four of 21 patients (19%) had difficulties in making friends, and rejection by peers was not considered to be a problem. This is in contrast with the results of our previously published studies in medulloblastoma and craniopharyngioma long-term survivors [19, 20]. Indeed, survivors of both medulloblastomas and craniopharyngiomas reported internalizing behavior problems in particular, with significant social problems. Survivors of both medulloblastomas and craniopharyngiomas showed physical sequelae of the tumor and/or its therapy such as alopecia, short stature, or obesity. These somatic problems can cause dissatisfaction with physical appearance and significant social withdrawal. However, survivors of cerebellar astrocytomas do not show physical sequelae. This fact may partly explain why social problems in survivors of cerebellar astrocytomas are less significant than in survivors of other brain tumors. Significant total scores of subjective behavior and emotional problems were found in four of 15 (26%) patients investigated. The behaviors that were described by the patients included anxiety, depression, and interpersonal sensitivity but also particularly psychoticism, hostility, and delinquent and aggressive behavior. These different neurobehavioral profiles could be grouped into two domains, reflecting either exaggeration or diminution of responses to the internal or external environment. Schmahmann et al. described these opposite behaviors in adults and children with both congenital and acquired cerebellar disorders as "dysmetria of thought" [37]. Impaired regulation of affect including irritability or impulsivity has been reported also by other long-term studies in survivors of cerebellar tumors [1, 4, 5].

According to the parent-rated CBCL, only one patient had a clinically significant total score of behavioral problems. On the internalizing behavior problems subscales, parents' ratings are more often clinically significant than patients' ratings. Similar results have been reported in survivors of other brain tumors [19, 20]. However, on the externalizing behavior problems subscales, parents' ratings are less clinically significant than patients' ratings. These findings contrast with the results published in studies about long-term survivors of other brain tumors [19, 20].

HRQoL of the 21 patients was analyzed by a self-reported, well-established HRQoL measure. Interestingly, patients with low-grade cerebellar astrocytomas rated their HRQoL as normal as or even higher than healthy controls. This is clearly in contrast to studies about HRQoL in patients with medulloblastomas and craniopharyngioma [19, 20]. These findings are also apparent in contrast with several published studies reporting long-term neurocognitive disturbances in children after surgery for cerebellar astrocytomas. It seems that long-term neurocognitive and behavioral problems (which are also noticed in some of our patients) have only a minimal impact on subjective quality of life. Emotional dysregulation was reported in acquired cerebellar lesions [37]. It is possible that this can modify the patient's judgement of their own quality of life. In addition, coping might play an important role. Adaptive mechanisms have also been considered in tetraplegic

patients following spinal cord injury, unexpectedly reporting better than average quality of life [38].

To our knowledge, this is the first study which comprehensively evaluates tumor control, functional and behavioral outcome, and their impact on social life and HRQoL in a population of patients with cerebellar astrocytomas treated with surgery alone. However, we are aware of important limitations in this study: the sample size is small; formal neuropsychological testing has not been performed in all patients, and two different tests were used for behavioral assessment because of age group limitations for each test. Despite a good quality of life after cerebellar astrocytoma treatment, careful long-term neurocognitive follow-up is needed in order to inform parents and teachers about the behavioral and cognitive sequelae and to contribute to timely social and educational intervention. We believe that this study will not only help to acknowledge the problems these survivors have to live with but also the good prognosis in terms of quality of life.

Appendix I: Semistructured interview questions

Diagnosis

How much do you know about your disease? Did you, or do you, take a particular interest in it?

Is there anything concerning your disease which is difficult for you? If yes, what?

Is there anything concerning your disease which was difficult for you and which you now consider to be less difficult? Or vice versa?

Present medication

Do you take any medicine now? Which ones? Are there medicines which you have taken in the past and which you do not take any more?

Are you disturbed by having to take these medicines every day?

Do you have, or have you had, any side effects due to the therapy?

Physical appearance

Are you satisfied with your appearance? What disturbs you most about your appearance? If you could, would you change anything about your appearance? If yes, what?

General body fitness–cognitive functions

Do you feel your physical ability is affected by your illness? How much?

Do you take part in any sport? Which one? Is there any sport you like but which you cannot take part in?

Can you concentrate well at school, at work? Do you believe your ability to concentrate has been impaired by your illness? What about your speed in solving tasks or in understanding new things?

Do you often have gaps in your memory?

Emotions

What positive feelings do you have towards your illness? What negative feelings about your illness?

Are you afraid of getting ill again?

School

Which school do you or did you attend?

How do you get on at school? Do you have any difficulties? If so, are they due to your illness? Do you like going to school? If yes, why?

How often do you not attend school?

Do you feel comfortable in your class?

Did anything change in your relationship to your schoolmates after your illness? If yes, what?

Have people in your school or at work been informed about your illness? Did you tell them about it?

Job

Which job did you train for or would you like to train for? Is this the job of your dreams?

Have you started an apprenticeship? Did you finish it? If not, why?

Did you, or do you, attend university?

What work do you do now? Are you happy with it? If not, why?

Did you have any other job before? Why did you change your job?

Hobbies

Do you have any hobbies? What are they?

Do you pursue your hobbies alone or with friends?

Are you a member of any club?

Do you play music?

Have you got a particularly strong interest in anything?

Do you have a pet?

Social situation

Do you live with your parents, with friends, or alone?

Do you live in a special home (hostel)?

How is your relationship with your parents or brothers and sisters? Do you often get angry with them? Would you prefer to live away from home?

Do you have a girlfriend or boyfriend or have you ever had one?

If you have no relationship: do you miss it? Can you imagine your future without a partner?

Do you have a good boyfriend or girlfriend? Are you in touch with him or her? How often?

How do you relate to your teachers–schoolmates–colleagues?

How do you relate to the doctor treating you? Who is he or she? Does he or she support you? Does he or she give enough time to you? Does he or she explain to you what he or she is going to do?

Are you independent in your daily life? Do you need help with particular things?

What is your source of income (wages–parents–state)? Do you receive a benefit? If yes, would you prefer any other source of income?

Future

How do you see your future?

What would you most like to happen?

Additional comments

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