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ORIGINAL PAPER

Long-term functional outcome of surgical treatment of juvenile pilocytic astrocytoma of the cerebellum in children

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Abstract
Purpose Increasing incidence of pediatric brain tumors and improving survival rates encouraged us to assess long-term functional outcome of patients with cerebellar juvenile pilocytic astrocytoma (JPA).
Materials and methods Our study encompassed 105 children treated since 1980–2005 and consisted in analysis of mailed, custom-designed questionnaires.
Results Mean follow-up time was 8.3 years. Sixty out of 104 patients presented permanent neurological deficits and 47/104 presented significant behavioral disorders. Eighty-nine children continued their education at primary, secondary or high school level. Most patients and their parents were satisfied with treatment outcome. Patients' and parents' notes were usually concordant.
Conclusions Long-term functional treatment outcome of cerebellar JPA is relatively favorable, in spite of permanent neurological deficits and emotional disorders in over half of the patients. Vermian tumors are associated with worse long-term functional outcome. Neurological deficits and emotional disorders do not preclude further education and independent functioning.

Keywords Juvenile pilocytic astrocytoma · Long-term treatment outcome · Children

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Introduction

Diagnosis of a brain tumor confronts patients and their families with a perspective of a life-threatening disease, severely compromising somatic, cognitive, and psychosocial functioning [1, 2]. Ultimate treatment outcome depends on the impact of disease itself, positive and negative effects of treatment, available support, and health-care facilities. On psychological and emotional level, the main source of anxiety is uncertain prognosis and limitations related to self-esteem, self-sufficiency, independence in everyday tasks, future professional performance and cohesion of family [3].

The key issue in neurooncology is the correlation of extent of tumor resection, patients' survival rate, and quality of life. Essentially, more radical cytoreduction is correlated with better cure rate and improved survival, but may be associated with unacceptable neurological deficits and poor quality of life [4]. This is particularly true in the case of tumors located in or close to eloquent brain areas. Significant progress in many fields of neurooncology achieved in the last decades resulted in a considerable improvement of survival rate associated therewith. Thus, the increasing importance of issues associated with quality of life, functional outcome of treatment, the patients' ability to cope with age-related roles, and duties and quality of life in general [5].

A sizeable body of data concerning quality of life of adult survivors of brain tumors is available, because these are several accepted and validated instruments enabling a reliable exploration of this issue. On the other hand, there are very few such studies concerning children due to conceptual and methodological difficulties. These are mainly caused by small and heterogenous groups of

patients and problems with obtaining reliable data from neurologically and cognitively impaired subjects [6, 7].

Aims of study

In view of relative paucity of data concerning long-term functional performance of pediatric survivors of brain tumor surgery, the purpose of our study were to assess long-term psychosocial functioning of children subjected to surgical treatment of cerebellar juvenile pilocytic astrocytoma and to define possible risk factors influencing long-term functional treatment outcome.

Preliminary results of this study have been presented at the XXI-st Meeting of the European Society of Pediatric Neurosurgery at Montreux, Switzerland, 11–15.05.2008.

Materials and methods

The study included children with the diagnosis of cerebellar juvenile pilocytic astrocytoma (JPA) treated at the Department of Neurosurgery of the Children's Memorial Health Institute, Warsaw, Poland, since 1980–2006. A uniform treatment protocol was adhered to: maximally radical excision and, in the case of recurrence, repeat surgery and radiotherapy. Within this time-span, 274 cases of cerebellar JPA were seen. Thereof, 162 children fulfilled inclusion criteria, i.e., at least 3 years follow-up and complete medical documentation available, enabling review of treatment course and contact with the patient and his/her family. In order to obtain data concerning current functional status of the patients, we used the "mailed questionnaire" technique. Custom-designed questionnaire addressed the current patient's condition, academic achievement, independence in everyday tasks, professional performance, and general satisfaction with treatment outcome. It included the following questions:

1. Have any other therapies (apart of surgery) been implemented, e.g., rehabilitation, non-conventional therapies, etc.;
2. Does the child present any neurological deficits (key features of cerebellar syndrome, pyramidal syndrome, bulbar syndrome, hydrocephalus, epilepsy, etc.)—explained in plain language, comprehensible to lay people;
3. Does the child require permanent medication (if so, what kind of drugs?);
4. Does the child present any behavioral disorders (irritability, hyperactivity, tearfulness, aggression?;
5. Does the child attend school (what type?), university, or is professionally active?;
6. Is the patient functionally independent (driving license, job, marriage);
7. How does the patient and his/her relatives rate (separately) the outcome of treatment (very good, good, satisfactory, poor, very poor).

The questionnaire was mailed to 162 patients. We received 105 filled-in forms (65%) and Three non-filled returns (change of address or addressee unknown).

Statistical analysis was performed using the STATISTICA PL v.5.0 software (StatSoft Poland). Data were analyzed using the Chi^2 Pearson's and the Student *t*-tests.

Results

Mean age of the patients at first diagnosis and surgery was 7.5 years (range 1–25 years) and there was a slight female predominance (male/female ratio, 51/54). Mean follow-up time was 8.3 years (range 3–22 years), but for most of our patients, this was 3–13 years. Therapeutic modalities implemented are presented in Table 1.

Based on information obtained, one patient died of disease. Therefore, all subsequent analyses relate to 104 responders. At the time of inquiry, 44 out of 104 patients were neurologically intact, while various types of neurological deficit were present in 60 out of 104 patients. Prevalence of particular symptoms is presented in Table 1. Neurological deficits, particularly dysequilibrium and bulbar syndrome, were more often associated with vermian tumors than with hemispheric tumors (Pearson $Chi^2 = 5.97$; $p=0.01$).

In order to check if there is any correlation between long-term functional results and date of surgery, we extracted patients operated on in the years 1980–1995 (the "early group"; $n=20$) and those operated on in the years 2000–2005 (the "recent group"; $n=33$). Long-term functional outcome, i.e., presence or absence of neurological deficits in the long-term follow-up are presented in Tables 2 and 3. Proportion of neurologically intact patients is nearly

Table 1 Therapeutic modalities implemented in patients with cerebellar JPA

Modality	No. of patients (total = 105)
Tumor excision	105
CSF shunt	4
Rehabilitation	51
Non-conventional therapies[a]	5

[a] i.e. herbs, acupuncture, hypnosis, mental energy, chiropractics, etc. (the latter figure may be underestimated, due to unwillingness of all concerned to report on such activities)

Table 2 Prevalence of permanent neurological deficits in JPA survivors

Neurological deficit	No. of patients (total n=104)
Dysequilibrium	48
Limb paresis	21
Strabismus	21
Ataxia	11
Bulbar syndrome	11
Epilepsy	4
Active hydrocephalus	4
Monocular blindness	1
Death	1

identical (55% vs. 57.5%), so, no worthwhile improvement of functional outcome has been obtained.

In our patient population, 96/104 were medication-free, while nine persons were on chronic medication (anti-epileptic drugs, $n=5$; artificial tears, $n=3$; piracetam, $n=1$).

Functional status of the patients is summarized in Table 4. Nearly half of the patients (52/104) do not demonstrate any significant or bothersome behavioral disorder (in their parents' opinion), while significant behavioral disorders of various types were present in the remaining 47 cases, in five cases no data were provided.

At the time of the study, 89 children were following normal academic curriculum (either at primary, secondary (high) or university level), three attended special schools and 12 did not attend school at all. Among patients who reached adulthood, 14 were studying at a university and 13 were professionally active. Only two adults did not study nor work. Fifteen patients have obtained driving license and four have established a family of their own. Only nine persons received a permanent disability pension.

Most patients and their parents consider the outcome of treatment as either good or very good. A summary of parents' and patients' satisfaction with treatment outcome is presented in Table 5. Correlation between parents' and patients' opinion on treatment outcome depending on presence (or absence) of neurological deficits is presented in Table 6. Correlation between parents' and patients' opinion on treatment outcome depending on presence (or absence) of behavior disorders is presented in Table 7. Graphic representation of concordance of parents' and patients' opinions is presented in Fig. 1. Patients' and parents' notes were concordant in most cases and in the entire group the correlation coefficient thereof was 0.69. Patients were rather more critical about their condition than parents. No data were obtained in 12 cases

Table 3 Long-term neurological function in JPA survivors depending on timing of surgery (years 1980-1995 vs. years 2000-2005)

	1980–1995	2000–2005
Neurological deficit present	9	14
No neurological deficit	11 (55%)	19 (57.5%)
Total	20	33

Table 4 Behavior disorders in long-term JPA survivors (individual items sum up to more than 104, as some children present several disorders; in some cases disorders did occur but were not severe enough to compromise everyday activity)

Behavioral disorder	No. of patients (total $n=104$)
None or mild	52
Irritability	62
Hyperactivity	24
Tearfulness	18
Aggression	1

Discussion

Juvenile pilocytic astrocytoma (JPA) of cerebellum is a relatively frequent pediatric brain tumor, where radical excision is considered curative and in general opinion is associated with a relatively favorable prognosis. The five year survival rate is estimated at 92% and 25-year survival rate 88 % [8, 9]; this being also confirmed by our observations. Most children with such a diagnosis will most probably reach adulthood, so important questions arise concerning long-term sequels of the disease and its treatment and their impact on the patient's future functional performance. We wanted to confirm these findings, focusing on a fairly homogenous group of patients in terms of tumor type, location and therapy implemented. We designed a simple questionnaire, comprehensible by an average lay person, addressing issues of daily living,

Table 5 Patients' vs. parents' satisfaction with long-term treatment outcome

Treatment outcome	Parents' opinion		Patients' opinion	
	N	%	*N*	%
Very good	63	60.5	38	36.5
Good	37	35.5	52	50
Satisfactory	1	0.96	3	2.9
Poor	1	0.96	1	0.96
Very poor	0	0	0	0
No data	2	1.9	10	9.6

Table 6 Patients' vs. parents' satisfaction with treatment outcome

	Parents		Children	
	Neurologically intact	Neurological deficits present	Neurologically intact	Neurological deficits present
Very good	90%[a]	37%[a]	79%[a]	14%[a]
Good	10%[a]	59%[a]	19%[a]	80%[a]
Satisfactory	0	2%	2%	4%
Poor	0	2%	0	2%
Very poor	0	0	0	0

Impact of permanent neurological deficits

[a] Difference in satisfaction with long-term treatment outcome depending on neurological performance was significant both in the group of parents and in patients. Parents: Pearson's $Chi^2 = 28.20$; patients: Pearson's $Chi^2 = 38.36$. For both, $p<0.01$

proficiency in everyday tasks, and educational demands. We wanted to explore a specific segment of pediatric brain tumor population and there are no validated Polish tools addressing in this field. In total, 162 questionnaires have been mailed and we received 105 filled-in returns (65 %), which is a normal result in this type of studies.

The last decade witnessed a dramatic progress in our understanding of neurophysiological role of cerebellum, confirming its significant role in co-ordination and regulation of cognitive and emotional processes and behavior [10, 11]. There are reports of permanent dysfunction in this area in patients undergoing resection of a cerebellar tumor in childhood [11–13]. It appears that such a dysfunction is associated with focal cerebellar damage caused by tumor and surgical intervention, and is not due to adjuvant chemoradiotherapy or other associated factors.

Most JPA survivors are able to resume and continue a normal academic curriculum at age-matched level. Upon reaching adulthood, they study at universities, are professionally active and establish their own families. Thereof, it might be concluded that the disease and its treatment did not result in any significant sequels compromising the patients' quality of life. Unfortunately, the truth is far less optimistic. Over half of the patients present permanent neurological deficits, usually in the form of dysequilibrium and ataxia, which significantly compromise their motor performance. Nevertheless, these patients manage to function nearly normally in everyday life [14]. A noteworthy and disturbing finding is that in spite of the above-mentioned relatively high incidence of postoperative neurological deficits, only about half of the patients entered some type of postoperative rehabilitation programs. It appears that an early, aggressive and comprehensive rehabilitation might significantly contribute to improve late outcome of treatment and the patients' quality of life.

JPA is considered one of the most prognostically favorable conditions in the entire pediatric neurooncology. Therefore, such a high proportion of patients presenting neurological deficits is surprising, but the facts speak for themselves. Furthermore, no worthwhile improvement has been observed over time, in spite of obvious progress in diagnostics, surgical technique, postoperative care and surgeons' expertise over the past 25 years. This is certainly an alarming sign, indicating urgent need for corrective

Table 7 Patients' vs. parents' satisfaction with treatment outcome

	Parents		Children	
	Normal behavior	Disorders of behavior	Normal behavior	Disorders of behavior
Very good	68%	51%	59%	26%
Good	32%	45%	41%	64%
Satisfactory	0	2%	0	7%
Poor	0	2%	0	3%
Very poor	0	0	0	0

Impact of behavior disorders

Difference in satisfaction with treatment outcome depending on normal behavior or disturbed behavior was significant only in the group of patients. Parents: Pearson's $Chi^2 = 4.48$ ($p=0.21$); children: Pearson's $Chi^2 = 12.67$ ($p<0.01$)

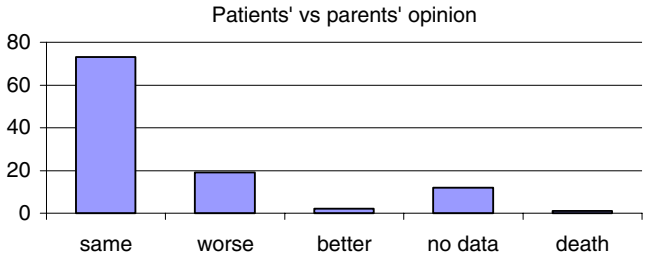

Fig. 1 Graphic representation of difference between patients' vs. parents' opinion on late outcome of treatment

action to be taken. It is also possible that general opinion concerning good outcomes of surgical treatment of cerebellar JPA is basically wrong and that the issue requires an honest and in-depth verification.

Only a small proportion of our patients (3%) attended special educational facilities. This confirms satisfactory cognitive development of these children in spite of the above-mentioned neurological deficits present. On the other hand, our results indicate a relatively high incidence of emotional dysfunction, which was present in over 50% of the patients. Most common findings include: irritability (i.e., prevalence of negative mood, tendency to react by irritation or anger to emotionally neutral stimuli), agitation, and tearfulness. These symptoms may attest to emotional instability and emotional dysregulation, which are frequent sequels of cerebellar lesions and considered common components of the cerebellar cognitive–emotional syndrome [11, 15].

An important prognostic factor is tumor location: vermian lesions were significantly more often associated with permanent neurological deficits. On the other hand, there was no correlation of tumor location with emotional dysregulation, which was clearly discordant with other authors' findings [13, 16]. This may be a result of different selection criteria adopted: these authors' results are based on relatively small samples of children with cerebellar tumors of very different histological types (JPA, ependymoma, medulloblastoma), with a clear correlation between tumor type and location (JPA was more often located in cerebellar hemispheres, while medulloblastoma was mostly associated with vermian location). Furthermore, in the case of essentially malignant tumor, we must account for adjuvant oncological treatment, which also has a confirmed deleterious effect on cognitive function. Therefore, it is difficult if not impossible to state, which factor was the key determinant of emotional functioning of these children [14, 17].

Patients' and parents' evaluation of treatment outcome is largely concordant, but in some cases differences are noticeable. In the case of discrepancy, the patients' note was usually worse than the parents'. Satisfaction with treatment outcome was mainly dependent on integrity of CNS function: parents of children with permanent deficits and patients themselves assessed treatment outcome worse than those neurologically intact and this is fairly obvious. An interesting finding was that parents tend to attach less importance to behavioral disorders: there was no significant difference in the opinion on treatment outcome among parents of children with and without behavioral disorders. They are happy that their children survived a potentially lethal disease. On the other hand, emotional problems are very important for patients themselves, as adolescent patients become increasingly aware of their limitations, distinctness from their peers and experience more painfully sequels of past disease and it's treatment. Patients with permanent behavior disorders consider long-term treatment outcome significantly worse than those who function normally. This may be explained as follows: young people consider emotional problems and difficulties in social functioning associated therewith particularly bothersome, as they concern an essential area of life. Also, greater negativism itself may be a result of depressed mood and irritability associated with disease- and therapy-related brain damage. Young people are generally more critical about themselves and the surrounding world; and this applies not only to teenagers who survived a lethal disease. Such differences are reported in studies concerning quality of life of healthy children too [17].

This study was performed using the technique of mailing. Filled-in questionnaires were obtained from 65% of the addressees, which is a typical result in this kind of studies. It is impossible to determine the fate of patients who did not respond. This group may well include patients in a poor overall condition, those dead from disease or unrelated causes (e.g., traffic accident), as well as symptom-free persons, considering past disease and surgery as a closed history which should not be revived. It is therefore difficult to state unambiguously to what extent our study population is representative and our analysis—reliable. Nevertheless, relatively large sample size and its diversity make us realistically hope that the results presented reflect the truth [2, 18].

There is paucity of data available, addressing the issue if quality of life in pediatric survivors of brain tumor. Problems associated therewith are due to heterogeneity of locations, malignancy grade, type of therapy implemented, wide range of patients' age and small series analyzed. Another source of problems is lack of verified and certified investigation instruments and inconsistent ability of pediatric patients to provide reliable data. We explored the problem, selecting a homogenous group of patients according to tumor type and locations, i.e., the key determinants of treatment outcome. We also used a custom-designed questionnaire, addressing such areas as current neurological

and behavioral status, general functioning level (education, driving license, occupation). In view of the existing limitations, we could not resort to the existing batteries, inventories and questionnaires, assessing quality of life, as a mailed questionnaire had to be short, straightforward, and understandable by average lay people in order to ensure an acceptable rate of filled-in returns [5, 7].

Our material indicates a relatively good adaptation of patients and their families to the disease and its sequels. In spite of neurological deficits and emotional disorders present, most children, adolescents, and young adults who underwent excision of a cerebellar JPA lead a close-to-normal life—attend schools, go to universities, start working, obtain a driving license, and become functionally independent. Even accounting for several methodological draw-backs, our study may serve as a good starting point to a more broad-based study on long-term functional outcome of pediatric survivors of brain tumors. This might have a significant prognostic value, both for health-care providers, patients and their families, enabling a realistic yet constructive approach aiming at enhancing developmental potential of children with brain tumors.

Conclusions

1. Long-term functional outcome of surgical treatment of children with cerebellar juvenile pilocytic astrocytoma is relatively favorable, although over half of the patients present permanent neurological deficits (mainly dysequilibrium) and emotional disorders (mainly irritability);
2. Vermian tumor location is associated with worse late functional outcome.
3. In most patients, neurological deficits and emotional disorders do not constitute a prohibitive obstacle in continuing education and independent functioning in adulthood.
4. Patients' and parents' opinions on treatment outcome are generally concordant, although patients tend to rate it worse than their parents.
5. Small proportion of children with neurological deficits included in rehabilitation programs shows promise for improvement in this area.

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