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Cognitive and Psychological Outcomes in Younger vs. Older Children with Subtentorial/Supratentorial Ependymoma after Radiation Therapy

Geraldina Poggi[1], Annarita Adduci[1], Lorenza Gandola[2], Susanna Galbiati[1], Alessandro Degrate[1], Elena Sironi[1], Sandra Strazzer[1], Maura Massimino[2]
[1]*Scientific Institute E. Medea, Bosisio Parini, Italy*
[2]*National Tumor Institute, Milan, Italy*
E-mail: *geraldina.poggi@bp.lnf.it*
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Abstract

Purpose: to investigate cognitive and psychological problems in children treated for intracranial ependymoma, the evolution of these disorders over time and the role of age at radiotherapy and tumor site, in their onset and persistence. **Methods and Materials:** 23 patients received a complete evaluation; some of them underwent follow-ups. The clinical data collected included sex, age (at diagnosis, assessment and tumor treatment, thus dividing patients into two cohorts: younger or older than 5 years), site (supratentorial vs. subtentorial), the presence of hydrocephalus, neurological examination, tumor treatment. All the patients received an age-appropriate cognitive and psychological evaluation. **Results:** The mean cognitive level was within the norm, with lower scores on the Performance Intelligence Quotient (PIQ). The psychological assessment revealed Internalizing problems and impaired independence. Children older than 5 years had a lower Intelligence Quotient (IQ) than the younger children, both at the initial evaluation and at follow-ups. Initially, the supratentorial group appeared to be less impaired than the subtentorial group but then exhibited a progressive decline in the IQ. In the subtentorial group, the children with an IQ within the normal range remained stable at the follow-up, while the children with below-norm scores at the initial evaluation showed deterioration over time. **Conclusions:** Tumor site seems to affect the cognitive outcome to a greater extent than age at radiotherapy.

Keywords: Cognitive Outcome, Ependymoma, Children, Radiotherapy

1. Introduction

Studies on the cognitive outcome of patients with ependymoma are limited in number and are generally part of larger studies where ependymomas are compared with other posterior fossa (PF) tumors such as medulloblastomas and astrocytomas [1-4].

The most recent studies on cognitive and neuropsychological outcomes show that patients treated for ependymoma do not present with severe cognitive impairment as compared to other brain tumors, even though many of them have neuropsychological problems (affecting memory, attention, language and executive functions) which often impair formal learning [5,6].

As for all brain tumors, age at diagnosis and the quality of surgery and radiotherapy are considered to be the most important predictive factors for the onset of cognitive and neuropsychological problems which have a great impact on long-term survival [7-11].

The impact of radiation therapy was explored in Merchant's studies which showed how Conformal Radiation Therapy (CRT) pointed out that supratentorial tumor location, multiple surgery, male sex, longer symptomatic interval, pre-CRT chemotherapy, endocrine deficiencies, hydrocephalus, and young age at CRT were predictive factors for academic problems [12-17].

In a recent work on 23 patients treated with local posterior fossa irradiation who received one or more consecutive neuropsychological evaluations, von Hoff found a moderate impairment of intellectual functions and identified early disease manifestation and treatment and postoperative neurological deficits as the main risk factors

for the onset of cognitive problems. This study also emphasized that the neuropsychological difficulties can vary in type and that no distinctive pattern of impairment can be identified, unlike in other tumors [18].

The present study thus set out to:

1) Define the influence of age at radiotherapy as a predictive factor by comparing two subgroups according to age at radiotherapy (children younger than 5 years and children older than 5 years).

2) Define the influence of tumor site as a predictive factor by comparing two subgroups according to supra- or subtentorial site.

3) Define the cognitive and psychological evolution of the whole group's cognitive profile over time.

2. Material and Methods

Patients

This study included the newly diagnosed patients treated for ependymoma at the Pediatric Oncology Department of the National Institute for Tumors of Milan in the time period between 1993 and 2005, according to two consecutive national AIEOP (Italian Association of Pediatric Hematology and Oncology) protocols.

In the 1994-2001 period, the patients with complete tumor excision received hyperfractionated radiotherapy (1.1 Gy twice a day) to the tumor bed plus 1 - 2 cm margins up to a total dose of 70.4 Gy. When the residual tumor was documented after surgery, the patients first received 4 chemotherapy courses with vincristine, etoposide and cyclophosphamide (VEC) plus/minus second-look surgery, followed by the same radiotherapy schedule (protocol 1) [19]. After 2001, the children with complete tumor excision and grade 2 revised histology received conformal radiation with conventional fractionation of 1.8 Gy/d up to a total dose of 59.4 Gy. The children with complete tumor excision and grade 3 revised histology received 4 VEC courses after radiotherapy. In the presence of a residual tumor, of any grade, VEC was prescribed before radiotherapy to facilitate second-look tumor removal. In the event of there still being a tumor after the second-look surgery, radiotherapy was completed with a boost delivered in two daily fractions of 4 Gy (protocol 2). Exclusion criteria included a history of previous brain lesions (congenital or acquired), pre-existing acute or chronic serious illness and psychomotor delay, as reported by the parents. All the patients received at least one complete cognitive evaluation.

A total of 23 patients were included in the study. After the initial assessment, some patients underwent further evaluation: 13 patients were assessed only once, 10 patients twice, 6 patients 3 times and 4 patients 4 times.

The progressive reduction in number in the patients participating in the follow-ups is due to that fact that about half of the 23 patients initially evaluated lived at a significant distance from their oncological centers and our Institute to which they had been referred for a multidisciplinary clinical and functional evaluation at the end of tumor treatment. These patients were then referred to more easily accessible centers and did not undergo later follow-ups.

All the participants gave their consent. The following clinical and medical data were collected for all of them: sex, age at diagnosis, age at assessment, age at tumor treatment, time between diagnosis and assessment, histological diagnosis, tumor site (supratentorial vs. subtentorial), hydrocephalus, neurological examination and type of tumor treatment (neurosurgery, chemotherapy and radiotherapy).

3. Methods

Cognitive/Neuropsychological and Psychological Evaluation

All the patients received an age-appropriate clinical cognitive and psychological evaluation.

The cognitive assessment was performed using the Wechsler Intelligence Scales-WPPSI-R, WISC-R [20, 21]. Attention, memory, executive functions, were also evaluated by age-appropriate tests (see **Table 1**).

The use of different tests did not allow for a quantitative analysis of the neuropsychological evaluation: for that reason, in this study, the only variable considered is the presence or the absence of specific problems in those investigated areas (attention, memory, executive functions). Thus, a qualitative analysis was performed.

The psychological evaluation protocol was geared to assess several aspects of psychosocial functioning. The *Child Behavior Checklist* (*CBCL*) [22] and the *Vineland Adaptive Behavior Scales-Expanded Form* (*VABS*) [23] were administered.

4. Statistical Analysis

Statistical analysis was conducted using SPSS software.

Table 1. Neuropsychological domain and test of measurement.

Neuropsychological domain and test of measurement	
Attention	• Conners' Kiddie Continuous Performance Test (K-CPT) • Continuous Performance Test II (CPT II)
Memory	• Rey Figure – memory – • Corsi Block – Tapping Test • Digit Span
Executive Functions	• Wisconsin Card Sorting Test (WCST)

Data are presented as means and standard deviations (SDs) for quantitative variables, and as frequencies and percentages for qualitative variables. The scores of some neuropsychological tests were transformed to Z-Scores. A Z-score ≥ 2 was considered to be pathological.

With regard to the associations between cognitive-psychological problems and site and age at radiotherapy, the findings were compared by means of an Analysis of Variance (ANOVA): multiple comparisons between subgroups of patients were performed based on age at radiotherapy, site. A matched-pair *t*-test sample compared the different evaluation outcome within the whole group. A p value < 0.05 (two-tailed) was considered to be significant.

5. Results

Sample Description at 1st Evaluation

Table 2 shows the demographic and clinical characteristics of the whole group (23 patients) at the first evaluation.

As shown in **Table 2**, most of the patients had been treated for a subtentorial ependymoma. Of these patients, 26% had developed hydrocephalus at tumor onset. Most of the patients were treated according to Protocol 2. The most frequently reported outcomes include motor problems, while sensory problems were found in a small number of patients. No patient presented with epilepsy.

With regard to the cognitive evaluation, at the initial assessment the group presented with mean Full Intelligence Quotient (FIQ), Verbal Intelligence Quotient (VIQ) and Performance Intelligente Quotient (PIQ) scores within the norm, although four (17.4%) patients had an FIQ below the norm.

In the neuropsychological test, 9 (39.1%) patients showed attention problems, 5 (21.7%) patients had memory problems and 9 (39.1%) patients had executive function deficits.

With regard to the psychological evaluation, the most frequently reported problem on the CBCL is Internalizing: 6 (26%) patients scored above the norm on the "Internalizing" scale. The VABS shows a greater impairment in the motor domain and independence. **Table 2** also shows the mean scores obtained by the patients in the psychological tests.

- **Age at Radiotherapy**

When radiotherapy was administered, 10 (43.4%) children were aged < 5 years and 13 (56.5%) children were aged > 5 years. When looking at the relationship between age at radiotherapy and cognitive outcome, there is a marked, yet not statistically significant, difference in IQ between the two groups: the older children have a lower mean IQ than the younger children. The difference in FIQ is close to significance ($p = 0.07$). With regard to the relationship between age at radiotherapy and psychological outcomes, the mean CBCL scale scores of the two groups are similar. In contrast, the VABS scores show a greater impairment in the older group, but this difference is not significant.

- **Tumor Site**

With regard to the supra-/subtentorial distinction, the initial cognitive evaluation revealed a greater impairment in the subtentorial group, with VIQ, PIQ and FIQ scores of 99.25, 91.58 and 96.6 in the subtentorial group and 102, 105.6 and 105 in the supratentorial group. The greater impairment of the subtentorial group appears to be confirmed by the VABS scores evidencing an impairment in independence and social skills. In contrast, the CBCL scores do not show any relevant differences.

6. Evolution over Time

To study the cognitive, neuropsychological and psychological outcomes evolution over time we opted for a qualitative analysis because of the attrition in the number of patient participating to this research; we performed a qualitative evaluation of each individual case and gave a description of the progress over time in the 11 cases undergoing follow-ups (see **Table 3**).

With regard to the initial evaluation, most cases were within the norm: 20 patients had an IQ of over 75, but three patients had a score below the norm; 11 patients showed neuropsychological difficulties, but only 7 patients showed a deficit in all neuropsychological areas. 10 patients had psychosocial problems.

With regard to progress over time, 6 patients remained stable or improved, and in all 6 cases these patients had a history of subtentorial tumors. However, we noticed a decline in the cognitive level of 5 patients at follow-up. Of the latter, almost all (4 patients) had a supratentorial tumor. The 5th patient had a subtentorial tumor. Unlike the other cases who had average scores at the initial evaluation, he already had an impaired cognitive level attributable to neurological lesions and sensory impairments which appeared after hydrocephalus at the tumor onset and neurosurgery.

Of the 5 patients whose condition worsened, two belonged to the group of patients aged less than 5 years at radiotherapy and three belonged to the group of patients aged more than 5 years at radiotherapy.

With regard to the site, we observed a tendency towards deterioration in patients with a supratentorial tumor and a tendency towards stability-rather than an improvement in those with a subtentorial tumor, regardless of age. The qualitative analysis revealed that site had a greater influence than age on the progress of the cogni-

Table 2. Sample description at 1st evaluation.

DEMOGRAPHIC AND CLINICAL DATA (23 patients)		
Demographic Data	Sex	Male: 13 (56.5%) Female: 10 (43.5%)
	Mean age at Diagnosis	5.66 years (SD: 3.86)
	Mean age at Radiotherapy (years)	6.09 years (SD: 3.89)
	Mean Time Diagnosis - Radiotherapy	0.34 (SD: 0.30)
	Mean Time Diagnosis - 1st Evaluation	1.86 (SD: 2.63)
	Age at 1st Evaluation (23 pt)	7.48 (SD: 4.29.)
	Age at 2nd Evaluation (10 pt)	8.27 (SD: 4.58)
	Age at 3rd Evaluation (6 pt)	8.81 (SD: 4.17)
Clinical Data	Tumor Site	Supratentorial: 6 (26.1%) Subtentorial: 17 (73.9%)
	Hydrocephalus at onset	Yes: 6 (26.1%) No: 17 (73.9%)
	Epilepsy	0 (0%)
	Sensory Deficits	Reduced Visual Acuity: 1 (4.3%) Strabismus: 2 (8.6%) Reduced Hearing: 2 (8.6%)
	Neurological examination	Hemiparesis: 5 (21.7%) Ataxia: 8 (34.7%)
	Radiation therapy	Protocol 1: 7 (30.4%) Protocol 2: 16 (69.6 %)
	Surgery	Total excision at first surgery 16 (69%) At second surgery 2 (8,6%)
	Chemotherapy	Yes: 12 (52.1%) No: 11 (47.9%)
COGNITIVE NEUROPSYCHOLOGICAL AND PSYCHOLOGICAL EVALUATION		
	FIQ	98.39 (SD: 19.02)
	VIQ	100.06 (SD: 18.2)
	PIQ	95.71 (SD: 21.53)
CBCL	Internalizing	55.69 (SD: 10.9)
	Externalizing	48.19 (SD: 7.9)
VABS	Communication skills	90.8%
	Daily Living skills	87.5%
	Socialization	90.7%
	Motor Skills	91.6%

tive situation over time.

7. Discussion

We studied the clinical and cognitive, neuropsychological and psychological profiles of patients in order to reveal how age at radiotherapy and tumor site have influence in defining this profile, describing how this evolve over time.

As compared to other populations, our sample fares better from a clinical point of view in that our patients did not exhibit severe motor or cognitive impairments. Their outcomes are definitely more favorable than that of patients who received whole brain irradiation [1-3]. The

Table 3. Qualitative analysis.

PT	Age at Diagnosis	Age at RT	Age at First Evaluation	Age Group	Tumor Site	IQ at First Evaluation	Cognitive Evolution over time	Attention Problems	Memory Problems	Executive Function Problems	Psycho-Social Problems
1	26	29	36	< 5	Supra	110	Deterioration	No	/	/	Yes
2	37	45	51	< 5	Supra	123	Deterioration	No	No	/	No
3	17	20	28	< 5	Sub	112	//	/	/	/	Yes
4	12	14	24	<5	Sub	102	//	/	/	/	No
5	19	22	30	< 5	Sub	98	//	/	/	/	No
6	27	39	45	< 5	Sub	91	//	/	/	/	Yes
7	37	37	39	< 5	Sub	101	Stable	/	/	/	Yes
8	42	47	48	< 5	Sub	134	Improvement	No	No	No	No
9	48	56	178	< 5	Sub	67	//	Yes	Yes	Yes	Yes
10	50	55	65	< 5	Sub	117	//	No	No	/	No
11	54	56	58	< 5	Sub	113	Improvement	No	No	No	No
12	60	63	68	> 5	Supra	98	Deterioration	Yes	Yes	Yes	Yes
13	65	67	72	> 5	Supra	107	//	Yes	No	No	No
14	103	105	131	> 5	Supra	95	//	No	No	No	No
15	170	176	187	> 5	Supra	97	Deterioration	Yes	Yes	Yes	Yes
16	60	64	73	> 5	Sub	70	Deterioration	Yes	Yes	Yes	Yes
17	63	66	144	> 5	Sub	86	//	Yes	Yes	Yes	No
18	68	82	92	> 5	Sub	101	Stable	Yes	Yes	Yes	No
19	72	73	156	> 5	Sub	93	//	No	No	Yes	Yes
20	103	105	112	> 5	Sub	54	//	Yes	Yes	Yes	Yes
21	117	119	118	> 5	Sub	90	Stable	Yes	No	Yes	No
22	132	134	150	> 5	Sub	115	Stable	No	No	No	No
23	180	182	185	> 5	Sub	105	//	Yes	No	No	No

LEGEND: RT = radiotherapy; SUPRA = supratentorial site; SUB = subtentorial site.

most frequently reported motor impairments included hemiparesis and ataxia in percentages similar to those reported in the literature [1,3,17]. They are almost totally attributable to a preoperative lesion or immediate post-operative lesion.

At the cognitive and neuropsychological levels, the mean scores of the whole sample are within the norm. The same holds true for the PIQ scores which were lower than the VIQ scores. The difference between PIQ and VIQ is consistent with the literature.

On the whole, the picture was stable from a neuro-psychological point of view as well; at the first evaluation, 4 of the 7 patients with significant neuropsy-chological problems had scored below or at the lower limits of the norm: these were patients with pre- or perioperative damage. 3 patients had neuropsychological difficulties which were associated with a subsequent deterioration of the cognitive level rather than an initial impairment. The neuropsychological problems did not appear to be necessarily associated to an impairment of the cognitive level. This is in line with recent reports of core problems (attention and memory problems) affecting academic performance, even in the presence of non-pathological cognitive levels [24,25].

It is assumed that disorders of attention, memory and executive functions—the functions underlying learning—impair the normal functional development process and, in so doing, affect contextual and school learning [26].

It is therefore necessary to perform repeat follow-ups over time as the presence of disorders affecting the basic

neuropsychological functions could adversely influence later cognitive development and planning, organization, categorization and cognitive flexibility, thus interfering with learning and interpersonal skills [24,25].

While investigating the outcome, relevant findings emerged when we divided the patients into groups according to age at radiotherapy and tumor site (supra- vs. subtentorial). With regard to age we found a greater cognitive impairment in the older patients at the initial evaluation than at the later follow-ups. Such a difference was seen in both performance and verbal tests.

With regard to tumor site, we found a greater initial impairment in patients with a subtentorial tumor, while patients with a supratentorial tumor showed a more favorable initial pattern which however deteriorated progressively at the follow-ups, both in performance and verbal tests.

In contrast, the subtentorial group remained stable or improved during time, except for the patient with scores below the limits of the norm at the initial cognitive evaluation who later exhibited a deterioration.

When looking at the most significant variables being studied (age, site), the limited sample size and heterogeneity does not enable us to draw representative conclusions on the differences in the clinical picture. However, it can be stated that the younger patients who were treated with radiotherapy do not appear to have a cognitive impairment. Only one out of 11 patients showed a generalized cognitive impairment, with an association between the below-the-norm IQ and neuropsychological psychological problems.

When interpreting this finding, it should be kept in mind that only 6/11 patients in the younger group underwent a neuropsychological evaluation (attention, memory and executive functions) because the remaining children were too young for these tests.

The most frequently observed psychological problems are Internalizing problems. The result of the psychological evaluation which was performed on our sample is in line with previous studies, which found the same kind of disorders affecting this population of patients.

In conclusion, we can safely state that, in our sample, tumor site seems to affect the cognitive outcome to a greater extent than age at radiotherapy.

This emphasizes the need for similar studies on larger samples which can provide a better insight into the multiplicity of cognitive, neuropsychological and psycho-logical profiles and enable a more detailed quantitative analysis to be made, together with more generalizable conclusions. Such studies should be long-term, as longitudinal observations enable better monitoring of the cognitive, neuropsychological and psychological problems and their impact on later cognitive development.

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9. References

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