ORIGINAL ARTICLE

Assessment of Neuropsychiatric Indicators in Children and Adolescents With Primary Brain Tumors and Other Brain Space-Occupying Lesions Before and After Surgery

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Abstract

Objectives

Cognitive abilities might be impaired due to brain lesions in children and adolescents. This study aimed to investigate neuropsychiatric indicators in children and adolescents with primary brain tumors and other brain space-occupying lesions (SOLs) before and after the surgical procedure.

Materials & Methods

The current pre-post study was conducted on 81 patients with brain SOLs aged under 18 years hospitalized in the Neurosurgery Ward of Imam Reza university hospital, Tabriz, Iran, within 20 December 2016 to 20 December 2017. The patients with metastatic brain tumors were excluded. Before and after the surgical procedure, Digit Span forward and backward task (to assess working memory), Stroop Task and Trail Making Task A and B (to assess attention), and Rey-Osterrieth Complex Figure Test (ROCF) (to assess visuospatial memory) were carried out. Then, the scores of the tests were compared to standard values and postsurgical scores.

Results

The most prevalent type of brain SOLs was medulloblastoma, and the most prevalent region of involvement was the posterior fossa. The scores of all tests after the surgery were significantly improved, compared to those before the surgery ($P<0.05$). In the assessment of Digit Span forward and backward task scores, there was no significant difference between the scores of patients before the surgery and standard values ($P>0.05$). Regarding the scores of various stages of the ROCF, the scores of the immediate recall stage were significantly

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low ($P<0.05$). Regarding Trail Making Task A and B and Stroop Task before the surgery, only Trail Making Task A and B scores were significantly increased ($P<0.05$). The scores of Trail Making Task A were significantly higher in patients with medulloblastoma and anatomically in left temporal tumors, which indicated greater damage to the attention field ($P<0.05$). In addition, in cerebellar tumors, the scores of the immediate recall stage of the ROCF were significantly lower than in other brain tumors or SOLs ($P<0.05$).

Conclusion

The visuospatial memory and attention of preoperative assessments were significantly impaired, compared to those of the healthy population ($P<0.05$). Working memory, visuospatial memory, and attention showed improvement, compared to those before the surgery. Deficits in the attention domain were greater in medulloblastoma.

Keywords: Brain Tumors; Neuropsychiatric Impairments; Visuospatial Memory; Working Memory; Attention
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Introduction

Brain tumors are the most common space-occupying lesions (SOLs) and simultaneously are the second most prevalent malignancy in children after leukemia (1, 2). Various brain tumors have wide differences in invasion and growth (3). Tumors of pediatrics are different from adults in various aspects in terms of the region and type of tumors. More than 50% of pediatric tumors are infratentorial; however, in adults, pediatric tumors are mostly supratentorial and about 25-30% infratentorial. In addition, most adult tumors are astrocytoma; nevertheless, about 40% of brain tumors among children are undifferentiated tumors (4, 5). The tumor complications have two general and regional aspects. General complications are mostly related to the increase in intracranial pressure, which is caused by tumor growth in a limited space. Regional complications indicate the brain regions which are near the tumors (5).

Due to the increase in life expectancy in patients, attentions are focused on various factors that affect brain tumors and improvement in the quality of life (4, 6). Patients might suffer from psychiatric problems, cognitive impairments, and physical illness (7, 8). Cognitive abilities are investigated through neuropsychological assessment and could be considered a baseline level compared to the conditions after an intervention. These abilities include attention, memory, executive functions, and visuospatial and linguistic capabilities (9). Brain tumors might reversely affect the neuropsychological functioning of the brain (10). There are several methods for the assessment of neuropsychological ability, such as Trail Making Task A and B (11), Stroop Task (12), Rey-Osterrieth

Complex Figure Test (ROCF) (13), and Digit Span forward and backward task (14).

Neuropsychological deficits have a negative effect on the quality of life of patients with brain tumors. Obtaining accurate information about the neuropsychological functioning level of patients is essential for planning the future supportive and rehabilitation measures (10). It is very important for patients to regain their premorbid functioning abilities; however, even subthreshold degrees of neuropsychological disorders might prevent this aim (15). It has been revealed that cognitive functioning is associated with the prognosis and risk of relapse, in which the potential for relapse is more precisely predicted, compared to imaging techniques (10). The current study aimed to investigate neuropsychological functioning in patients with brain tumors or other SOLs of the brain, referring to a neurosurgery clinic before and after the surgery. Additionally, this study examined the relationship between neuropsychological deficits with the anatomical location and the type of tumor histopathology.

Materials &Methods

This study was performed to explore neuropsychological deficits in patients with primary brain tumors and other brain SOLs before and after the surgery at Imam Reza hospital in Tabriz, Iran. A total of 81 children and adolescents entered the study by considering inclusion and exclusion criteria. The inclusion criteria were age under 18 years, diagnosis of primary brain tumors or other brain SOLs in the Neurosurgery Clinic of Imam Reza university hospital candidate for brain surgery, diagnosis time less than 6 months, the willingness of the patient, parents, or caregivers to participate in the study, passing at least 1 month to enter the assessment after the surgery, and lack of major complications after the surgery based on physician's diagnosis. The exclusion criteria were metastatic brain tumors, use of anticonvulsant and corticosteroid medications, concomitant physical disease, psychiatric treatments, and intelligence quotient (IQ) below 75 prior to the surgery.

2.1. Procedure

The present study was approved by the Regional Medical Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.178). This study was carried out at Imam Reza university hospital within 20 December 2016 to 20 December 2017, for which informed consent was obtained from all the patients.

Prior to the surgery, all the eligible patients were assessed by Raven's IQ test for basic cognitive status on the first day of admission. Then, if the score was higher than 75, neuropsychological tests, including tests of Digit Span forward and backward task, Trail Making Task, Stroop Task, and ROCF, were carried out by a trained psychiatry resident. One month after the surgery, the IQ tests and neuropsychological tests were repeated, and the results were compared to those before the surgery. Neuroimaging reports were studied through medical files to determine the sites of tumors. After the surgery, the precise location of brain SOLs was recorded based on the surgeon's report. In addition, the type of histopathology of the brain SOLs was determined based on the pathologist's report. The existence of any possible relationship between neuropsychological deficits with the anatomical site and the type of histopathology was examined.

2.2. Study Instruments

In this study, some of the tests of the Persian Paper and Pencil Cognitive Assessment Package were used to investigate the neuropsychological status of the patients.

Trail Making Task: It is a test to investigate set-shifting and attention. For the implementation of this test, the subject is asked to draw a path from 1 to 25 within the shortest possible time, whereby the time of this drawing is assessed. In another form of this test, the subject is requested to draw from 1 to 12 and A to L such that a periodic pathway would form between the numbers and letters, and again the time is recorded. In Canada, a study was performed to obtain the normal scores of this test in the healthy population in 2004; therefore, the average scores were obtained for every age group (17).

Rey-Osterrieth Complex Figure Test: It is a neuropsychological assessment in which the subject is asked to copy from a shape with a series of complex lines at first. In the next steps, the subject will be asked to use his/her memory to recover it and draw the shape again (18). This test is used to measure visuospatial memory with three stages, namely copying, immediate recall (re-drawing the shape after 3 minutes), and delayed recall (re-drawing the same shape after 30 minutes). Each stage is scored based on the shape drawn. Moreover, the time of the copying stage is recorded. Palmo et al. (2013) conducted the ROCF on 179 healthy individuals in different age groups. The goal was to normalize the scores related to this test (19).

Digit Span Forward and Backward Task: It is a part of the Wechsler Intelligence Scale for Children. In this test, a list of numbers is presented to the subject, and he/she is requested to repeat this list first forward and then backward. The longest number memorized and repeated by the individual is his/her Digit Span. These two tests are used to measure working memory. Orangi et al. in Iran performed the normalization of the Wechsler test on 205 subjects and determined the mean scores of the subjects for different age groups (reliability=0.74) (20).

Stroop Task: It is used to measure the ability of the subject to inhibit the dominant response. The dominant response inhibition is a process that inhibits the generation of immediate responses that are irrelevant to the task. In the first stage, the subject is asked to quickly read the words “red, green, blue, and yellow” printed in black. The second stage is divergence conditions, whereby, for example, the word “red” is written in green, and the subject is requested to name the word color and not read the word itself (e.g., the correct response is green). At every stage, the number of errors and duration of response are recorded. The interference score is obtained by subtracting the time of implementing the divergent conditions and the time of implementing the baseline stage. A high positive score in the interference score represents the more substantial role of interfering factors and increased working memory load under divergent conditions. This test has been used to measure attention. To date, various studies have been conducted inside and outside Iran using different types of Stroop Task. Nevertheless, as they have used the computer version of Stroop Task, their scores cannot be used for comparison to paper and pencil Stroop Task scores. Therefore, in this study, the preoperative and postoperative scores of the patients were compared for the measurement.

2.3. Data Analysis

Descriptive statistics and frequency are expressed based on numbers and percentages. The comparison of the frequency difference of cognitive disorders between the two assessments was conducted by the Chi-square test; nevertheless, the comparison of mean scores was carried out through the t-test. The One-sample runs test was used to investigate the relationship between the neuropsychological indicators with the pathology and anatomical location of tumors. The data were analyzed by SPSS software (version 23). In this study, a p-value less than 0.05 was considered statistically significant.

Results

In this study, 81 eligible children and adolescents hospitalized due to primary brain tumors or brain SOLs at Imam Reza hospital in Tabriz in 2017 were enrolled in the study. The mean age value of the patients was 11.67±3.95 years (range: 6-18 years) (Figure 1). There was no significant difference between the age groups of children and adolescents and the number of patients with brain lesions (P>0.05).

The One-sample runs test was used to compare the scores of the neuropsychological indicators in patients with brain SOLs before the surgery to standard criteria (Table 1). No significant difference was observed in the results of the Digit Span forward task, Digit Span backward task, Trail Making Task B, Stroop Task, ROCF copy time, and ROCF delayed recall in patients with brain SOLs before the surgery, compared to standard criteria (P>0.05). Trail Making Task A and ROCF recall scores in patients with brain SOLs showed a significant difference, compared to standard criteria before the surgery (P<0.05). The scores of Trail Making Task A and ROCF recall were higher and lower in these patients than in standard criteria, respectively.

The paired t-test or Wilcoxon test was used to compare the neuropsychological indicators in patients before and after the surgery. The scores of Digit Span forward task, Digit Span backward task, ROCF copy time, ROCF immediate recall, and ROCF delayed recall in patients after the surgery were significantly increased, compared to those reported before the surgery (P<0.05). The scores of Trail Making Task A, Trail Making Task B, Stroop Task, and ROCF copy time in patients after the surgery were significantly reduced, compared to those reported before the surgery (P<0.05).

Neuroimaging reports were studied through medical files to determine the sites of tumors. After the surgery, the precise sites of the tumors were recorded based on the surgeon's report. Table 2 shows the frequency of anatomical locations of brain SOLs in patients. The most prevalent involved region of brain SOLs was the posterior fossa.

Furthermore, the presence of any relationship between cognitive deficits and anatomical site of the brain SOLs was examined. No significant relationship was observed between forward and backward Digit Span tasks, Trail Making Task B, and ROCF copy score, copy time, and delayed recall with the anatomical site of brain SOLs (P>0.05). Trail Making Task A scores in patients with left temporal tumors were significantly higher than in other brain sites (P<0.05; Table 3). In addition, the score of ROCF immediate recall in patients with cerebellar tumors was significantly lower than in other brain tumors or sites (P<0.05).

This study also investigated the association between the histopathology of SOLs and changes in neuropsychological indicators. In the histopathology of SOLs, the scores of Trail Making Task A in patients with medulloblastoma were significantly higher than other brain tumors or SOLs, which showed greater damage to the attention area (P<0.05).

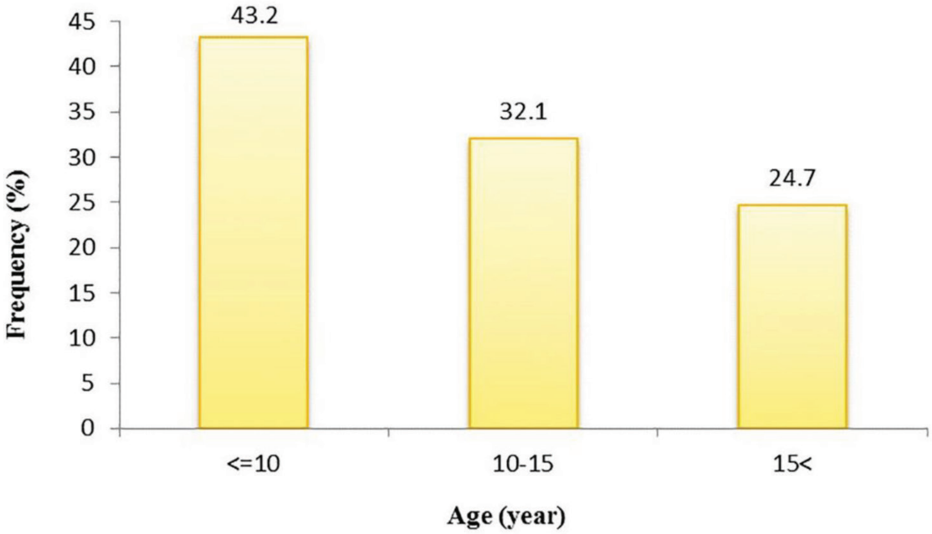

Figure 1. *Age Distribution of Patients*

Table 1. Comparison of Neuropsychiatric Indicators in Patients with Mean Values before Surgery

Neuropsychological indicators	Mean±standard deviation	P-value
Forward Digit Span	6.32±2.61	0.395
Backward Digit Span	2.86±1.6	0.348
Trail Making Task A	83.44±17.76	0.001>
Trail Making Task B	110.63±24.99	1
Rey-Osterrieth copy score	28.32±6.1	0.99
Rey-Osterrieth copy time	144.75±47.59	1
Rey-Osterrieth immediate recall	14.23±4.05	0.001>
Rey-Osterrieth delayed recall	10.34±3.44	0.58

Table 2. Frequency of Anatomical Locations of Brain Space-Occupying Lesions in Patients

Anatomical location	n	%
Posterior fossa	21	25.9
Intraventricular	11	13.6
Cerebellum	10	12.3
Right frontal	7	8.6
Left occipital	5	6.2
Left temporal	5	6.2
Right occipital	5	6.2
Right frontoparietal	5	6.2

Right frontotemporal	3	3.7
Right temporal	3	3.7
Left frontotemporal	2	2.5
Left frontal	2	2.5
Right frontotemporoparietal	1	1.2
Right temporoparietal	1	1.2

Table 3. Relationship between Trail Making Task A and Anatomical Location of Brain Space-Occupying Lesions

Anatomical location	**Trail Making Task A before surgery**	
	P-value	**Standard deviation±mean**
Cerebellum	0.095	94±15.24
Intraventricular	0.396	89.09±15.28
Left frontal	0.953	83±38.18
Left frontotemporal	0.374	88±2.82
Left occipital	0.062	69±2.82
Left temporal	0.044	70.2±11.36
Posterior fossa	0.343	81.1±18.87
Right frontal	0.981	84.86±15.25
Right frontoparietal	0.419	92.6±18.67
Right frontotemporal	0.356	71.33±19.85
Right occipital	0.317	78±13.71
Right temporal	0.649	92.33±23.96
Right frontotemporoparietal and right temporoparietal	0.731	94±20

Table 2 shows the frequency of the histopathological type of brain SOLs in patients. The most common brain SOLs was medulloblastoma (37%).

Table 4. Frequency of Histopathological Type of Brain Space-Occupying Lesions in Patients

Histopathological type	**n**	**%**
Medulloblastoma	30	37
Cyst	17	21
Astrocytoma	10	12.3
Schwannoma	3	3.7
Hemangioma	3	3.7
Glioblastoma	3	3.7
Ganglioma	3	3.7

Fibroblastoma	3	3.7
Neurinoma	2	2.5
Optic nerve	2	2.5
Lymphoma	1	1.2
Meningioma	1	1.2
Neuroblastoma	1	1.2
Craniopharyngioma	1	1.2
Neurofibroma	1	1.2

Discussion

In the present study, neuropsychological indicators were examined in patients with primary brain tumors and other brain SOLs before and after the surgery. For this purpose, 81 patients aged under 18 years were studied. This study examined the results of the neuropsychological tests, including Digit Span forward and backward task, copy score of ROCF, copy time of ROCF, immediate recall of ROCF, delayed recall of ROCF, Trail Making Task A and B, and Stroop Task. By comparing the scores of tests before and after the surgery, some indicators, including Digit Span forward and backward task, improved significantly after the surgery, suggesting ameliorated working memory in the patients after the surgical procedure. The scores of these tests before the surgery did not show any significant difference, compared to standard values; however, the scores suggested considerable improvement, compared to those reported for the preoperative condition.

In investigating the tests related to visuospatial memory, the scores of ROCF copy time, immediate recall, and delayed recall increased significantly, compared to those reported before the surgery; however, the copy time score of the ROCF diminished, compared to the baseline. This reduction in the copy time suggested improved response status. Therefore, the visuospatial memory of patients improved significantly after the surgery. The immediate recall score of the ROCF had a significant reduction, compared to the standard value, suggesting impaired visuospatial memory in these patients.

Additionally, Trail Making Task A and B and Stroop Task scores decreased, compared to those reported before the surgery, suggesting improved attention and set-shifting in patients after the surgery. In the preoperative investigation, only the Trail Making Task A score increased significantly, compared to the standard value, indicating potential attention deficits in these patients. In patients with medulloblastoma, the score of Trail Making Task A was significantly increased, compared to those of other types of tumors, suggesting a more severe impairment of attention in this tumor. Anatomically, in the tumors of the left temporal region, the Trail Making Task A scores were significantly higher, indicating more damage to the attention area in these patients. In addition, the scores of ROCF immediate recall in patients with cerebellar tumors were significantly decreased, suggesting a more severe impairment of visuospatial function in the tumors of this brain area. According to the findings of the present study, in patients with brain tumors or other brain SOLs, attention and visuospatial memory impairments were evident, compared to the healthy population.

In line with the results of the current study, in a study conducted by Robinson et al. (21) on working memory in patients aged 8-16 years with brain tumors, the functions of these individuals were considerably improved after the surgery, especially in patients with tumors in the anterior lobe. The sample size in the current study considerably differed from that of the aforementioned study (81 vs. 17 individuals). The most important difference between the two studies was the assessment time of this impairment. Accordingly, the current study investigated the status change of working memory of patients after the surgery; however, Robinson et al. investigated the long-term performance of the patients and examined patients at least 2 years after diagnosis and treatment.

In a similar study recently conducted by Barzilai et al. (22) to investigate improvements in cognitive deficits in patients with low-grade glioma, the surgery had no impact on the improvement of attention and working memory. Nevertheless, the present study showed that patients' cognitive performance increased significantly in terms of attention and working memory. It should be considered that the two studies were different in terms of methodology; Brazilai et al. employed Wechsler Adult Intelligence Scale-III Digit Span and Wechsler Memory Scale-III to measure attention and working memory; nonetheless, in the present study, Trail Making Task A and B and Stroop Task were used to measure attention. On the other hand, the location of tumors in the aforementioned study was not correlated with improvement after the surgery, which is in line with the results of the current study. Similarly, Satoler et al. indicated that glioma surgery is possible without long-term damage to cognition (23-24). In addition, several other studies have emphasized the benefit of surgery for the improvement of cognitive functions (25-26).

In a study with a similar method, average age, and distribution of tumors, Dwan et al. (27) investigated the neuropsychological status of patients (n=44) with brain tumors. Dwan et al. utilized the ROCF copy and recall, Trail Making Task B, and Hopkins Verbal Learning Test to examine memory, executive function, and attention. Moreover, a control group was employed for comparison. Different from the results of the present study, it was shown that neuropsychological functions were significantly impaired, compared to those of the control group in the areas of memory and executive functioning. Nevertheless, in line with the results of the current study, attention scores were lower than the control group. However, this difference was not statistically significant, different from those of the present study. In the current study, comparing the obtained results to standard values was used instead of using a control group.

The significantly lower scores of neuropsychological tests in patients with brain SOLs in the current study have also been confirmed by some other previous studies (28-29). Alongside the inclusion of tumors with different characteristics, other reasons that can justify the differences in different studies include using different tests to measure each of the neuropsychological functioning areas. It is possible to employ different tests to measure cognitive functions, which in turn causes different findings, thereby complicating the comparison of the results of different studies (30-31).

Despite the relatively large sample size, the diversity of the types of brain SOLs was one of the limitations of the present study. The participants with different types of brain SOLs with various manifestations were examined. Although the attempts were made to investigate the scores of tests for every individual site and histopathology in this study, the low sample size related to some brain locations and/or histopathology and the diversity in the number of frequencies might challenge the accuracy of the results regarding the associational inferences. Furthermore, the assessment of patients in frequent and long-term follow-ups can clarify the long-term effects of brain tumors, the outcomes of their operations, and consequences for neuropsychological functioning, an issue that can be considered another limitation of the current study.

In Conclusion

The severity and nature of neurocognitive deficits are key factors affecting the quality of life in patients with brain SOLs, highlighting the significance of measuring these indicators in these patients. In the present study, preoperative visuospatial memory and attention differed significantly from those of the healthy population; accordingly, all neuropsychological indicators significantly improved after the surgery, demonstrating the greater impact of primary brain tumors on these two indicators. The measurement of the aforementioned indicators before the surgery can inform therapists of the extent of functional impairments and provide them with a basic level of patient functioning.

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Author's Contribution

AM, ASh-K, HSh, ShA, AM, and FS contributed to the conception and design of the study. SN, AM, SF, FM, and SD contributed to the acquisition, analysis, and interpretation of the data. SN, AM, and ASh-K were the main contributors to writing the manuscript. All the other authors revised the manuscript critically for important intellectual content. All the authors read and approved the final manuscript.

Conflicts of Interest

The authors declare that the study was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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