

Computerized Addenbrooke's Cognitive Examination for Neurocognitive Monitoring of Children with Benign and Malignant Brain Cerebellar Tumor

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Abstract

Background: Brain tumors in the cerebellum site, especially in the cranial nuclei, are most commonly associated with cognitive impairment in children, but the differences in dimensions of cognitive impairments in pediatric benign and malignant tumors are rarely studied. Meanwhile, cognitive impairments in this area are required to be widely studied. This study aimed at using Computerized Addenbrooke's Cognitive Examination Revised (CACE-R) as an effective and new neurocognitive monitoring tool to diagnose children with benign brain tumors (BBT) and malignant brain tumors (MBT) after surgery.

Materials and Methods: In the present causal-comparative study, 83 children aged 10 to 14 years old with BBT and MBT, who were treated in Mahak (a pediatric oncology support center in Tehran, Iran) during 6 months, participated. They underwent surgery and fractionated radiotherapy (at a dose of 53 Gy). After meeting the inclusion criteria, they were evaluated by a computerized version of ACE-R.

Results: In this study, 33.33% of children with MBT vs 28.89% of BBT used shunts and 28.89% of them experienced relapse and 22.82% dropped out of school. About 17.77% of mothers were not graduated from high school. These factors predicted the memory, fluency, and language of these children. Furthermore, the results of this study showed a significant difference between children with BBT and MBT in terms of attention/orientation, memory, fluency, language, and visual-spatial abilities in ACE-R ($P < 0.001$).

Conclusion: Children with BBT compared with those with MBT experienced more problems in attention-orientation function, short- and long-term memory, fluency, language, and spatial-visual ability. These results emphasized that only leisure induced by tumor growth did not cause cognitive impairment, but the nature and function of the tumor also contribute to damage of the brain activity.

Keywords: Cerebellar, Children, Neoplasms, Neurocognitive

Introduction

The recent studies have shown that the incidence of brain tumors (as second common cancer in children) has increased in the past recent decades (1). Cancer treatment technologies improve life expectancy in children with cancer. In this way, the quality of life in children is in the first line of attention in health services. The cognitive performance, including memory, attention, ability to make decisions, and information process is an important part of the quality of life.

The cognitive and emotional disorders have been diagnosed in 23% of children with brain tumors. More than 90% of

children with brain tumors experience impairment in at least one cognitive area (2). Executive function, memory, and attention disorders are observed in 78% of the patients (3). The symptoms include impaired attention and concentration, delirium, amnesia, dementia, apathy, irritability, depression, or psychotic symptoms. The cognitive impairment and mental disorders are associated with many factors such as tumor location, tumor surrounding, drugs, radiation, chemotherapy, and patients' vulnerability (4).

Brain tumors are the most common solid tumors in children (5). A benign tumor

does not contain cancer cells and usually, once removed, does not recur. These tumors can; however, cause symptoms similar to cancerous tumors because of their size and location in the brain. Malignant brain tumors (MBT) are usually fast-growing and invade surrounding tissue. MBTs very rarely spread to other areas of the body but may recur after treatment (6).

Since 1936 that Wolf Son studied the mental consequences of the brain tumor in humans, there have been many studies on the consequences of tumor growth (7); however, there are still many obscure points in this area. Most tumors are associated with damage in cognitive, language, and memory functions (8). Usually, tumors create more psychiatric syndromes compared with other cerebrovascular diseases. Frontal and temporal tumors lead to most common psychiatric symptoms (9). Tumors in frontal lobes often lead to the progressive emergence of psychological changes such as weakness in reasoning, inappropriate social behavior, personality changes, poor planning, and dysfunction in Broca's area (10). Tumors in the temporal lobe cause memory weakness, hearing loss, inefficiencies in long-term memory, and difficulty in learning and understanding the language (deficit of Wernicke area). Many tumors located in the parietal lobe may lead to poor language interpretation, pain, and poor visual-spatial perception (11). A multitude of tumors related to occipital lobe creates weakness or loss of vision. Cerebellar tumors develop poor balance and muscle movement. Additionally, it may disrupt the non-verbal cognitive function such as spatial visualization and graphical abilities (12). In addition, Pineal region tumor causes attention deficit, visual disturbance, impaired memory, and problem-solving disability, and emotional disorders (13). The most common cognitive disruption among patients with glioma includes disturbance in attention and executive

function, visual-spatial (visual, 3-dimensional) and graphical skills, cognitive-emotional function, language, memory, and mental function (14). Cognitive disability is related to other dysfunction in general health such as fatigue, sleep disorders, and anger dysregulation in children with cancer (15). Several factors may lead to CI; for example, a personal history of psychopathology, especially in childhood, intensifies information processing dysfunction (16).

The cerebellar tumors in children, unlike adults, are very common (17). Benign tumors are widespread and slow growth. Surgery is used to treat this kind of tumors. Radiation therapy usually applies to malignancy and aggressive tumors. Tumors in the cerebellum site can lead to cognitive damages (18). For example, it is related to time perception and the speed of information processing. For this reason, the processing speed decreases in children with cerebellar tumors, and as a result, their intelligence quotient (IQ) decreases. In a meta-analysis, Shi et al. (19) demonstrated IQ, attention, processing speed, academic achievement, and career success were damaged in children with brain tumors. The severity of the cognitive impairment in malignant tumors is related to factors such as social support, developmental factor, and tumor and its treatment (20). The type of treatment (surgery, chemotherapy, and radiotherapy) can create side-effect in the post-treatment period, but the type of tumor may also play a role in cognitive function. In the present study, the treatment factor was controlled (21, 22). Factors affecting the outcome in the benign tumors are younger and radiotherapy is done. One of the limitations of the previous studies is the fact that these studies were based on parents' and teachers' reports. This research was an attempt to apply a simple instrument to evaluate cognitive deficit in children with BT.

Few studies compared cognitive impairments at MBT and benign brain tumors (BBT), and further research needs to reveal newer dimensions of discrepancy in two groups. Most studies have been done in this field are based on other reports (parents or nurses) and fewer children have been studied directly. In other cases, the research was done based on the child's report; it was performed in the post-treatment (survivors) or recovery period, while the present study involved participants during treatment.

However, this study controlled interfering factors to answer whether the nature of tumors (to be MBT or BBT) affects the severity of CI in patients with the brain tumor? In this study, patients with MBT and BBT were compared. This study considered the BBT and MBT as indicators to answer whether the structural and behavioral nature of cerebellar tumors damage cognitive function or not?

Materials and Methods

A causal-comparative design (for comparison groups) was used in this research. Eligible participants were recruited from a pediatric oncology hospital (Mahak) between January and March 2019 in Tehran, Iran. The participants aged between 10 to 14 years with the diagnosis of BBT and MBT. The sample size was 81 based on the Morgan table. The purposeful sampling method was used in this study. To identify eligible participants, the investigator interviewed 89 children, and 83 children (BBT [n= 38] and MBT [n= 45]) were accepted to participate in this study. Informed consent was obtained from all participants' parents. A computerized version of ACE-R was used to evaluate the cognitive impairment in children. The research objectives were explained to the patients or their parents. They were assured that they can leave the study at any time. The inclusion criteria were as follows: 1) the incidence of primary tumor, 2) age between 10 to 14 years old, and 3) underwent surgery 12 to

24 weeks before the study. The exclusion criteria included 1) having very bad physical condition, 2) having systemic diseases or illness except for brain tumor, 3) having a history of psychiatric disorders, which may interfere to answer questions such as ADHD or Autism, 4) receiving radiotherapy or chemotherapy, and 5) unwillingness to participate in the study. The ethics code of this article (IR.TUMS.VCR.REC.1397.779) was issued by Tehran University of Medical Sciences.

Addenbrooke's Cognitive Examination Revised Version (ACE-R)

ACE was developed as a diagnosing and screening instrument. It is able to distinguish between the types of dementia such as Alzheimer's (AD), forehead-temporal dementia (FTD), upper core progressive paralysis, and other Parkinson's syndromes and helps to detect CI in patients with the damaged brain (23). The revised forms of ACE have been used for clinical practice (24, 25). This instrument has been standardization and localization in Iran (26).

Addenbrooke's Cognitive Examination Revised Version (ACE-R) includes 5 sub-factors. Each of the sub-factors assesses a cognitive function. In ACE, the maximum score is 100; scores are allocated to the following sub-factors: attention/orientation (18), memory (26), fluency (14), language (26), and visual-spatial ability (16). ACE-R has been reported to have high sensitivity and specificities for the diagnosis of dementia.

The psychometric characters of ACE-R were assessed by 241 participants. Cut off scores of ACE-R with 95% confidence interval include: Accuracy (0.83 [0.76-0.90]), Sensitivity (0.96 [0.90-1.0]), False positive rate (0.28 [0.16-0.40]), Specificity (0.72 [0.60-0.84]), false negative rate (0.04 [-0.02-0.1]), positive predictive value (0.75 [0.63-0.86]), False alarm rate (0.05 [-0.02-0.1]), negative predictive value (0.95 [0.89-1.02]), Diagnosis odd ratio (DOR) (57.2), Positive likelihood ratio (LR+)

(3.44 [2.23-5.32]), and Negative likelihood ratio (LR-) (0.06 [0.04-0.09]). Two cut-off points (82, 88) were proposed based on sensitivity and accuracy. The Persian version of ACE was standardized based on Iranian culture in 2009. The Cronbach's alpha coefficient of all participants, control group, MCI group, and AD group was 0.84, 0.97, 0.88, and 0.93, respectively.

Statistical Analysis

Kruskal–Wallis, as a non-parametric test (no assumption) and Chi-square statistic (χ^2) were performed for data analysis.

Results

A total of 38 children with benign tumors and 45 children with malignant tumors participated in the present study. According to the findings of the current study, 53% of the patients were girls. The patients aged between 10 to 14 years old. Table I presents the number of patients based on the site of tumors and comorbidity disease. About 33.33% of children with MBT vs 28.89% of BBT

used Shunts and 28.89% of them experienced relapse and 22.82% dropped out of school. About 17.77% of mothers were not graduated from high school. These factors predicted the memory, fluency, and language of these children.

In Table II, the mean and standard deviation of the total score of ACE-R based on the type of tumor (BBT or MBT) are reported. The mean total score in the Adenbrook test in malignant tumor group was 64 with a standard deviation of 17.62 and the benign tumor group was 80 with a standard deviation of 15.42.

The results of the Kruskal–Wallis test displayed that in all dimensions of the Adenbrook test, the difference between the two groups (MBT and BBT) was significant at the level of 0.001.

Table IV shows a difference between MBT and BBT groups in all of the subscales. The MBT group, compared to BBT group, obtained a lower grade in all scales. This difference was significant in attention-orientation, memory, fluency, language, and spatial-visual ability ($P < 0.05$).

Table I: Classification of risk factors such as shunt, relapse, drop-up, and education of mothers according to tumor grade and sex

Variables		Tumor grade [n(%)]		Sex [n(%)]	
		MBT	BBT	Girls	Boys
Shunt	yes	15 (33.33)	4 (8.88)	7 (8.43)	12 (14.45)
	No	30(66.66)	34 (75.55)	35 (42.16)	29 (34.93)
Relapse	yes	13(28.89)	0 (0)	5 (6.02)	8 (9.63)
	No	32(71.11)	38 (84.44)	41 (49.39)	29 (34.93)
Drop-out (quit school)	yes	37(82.22)	10 (22.22)	23 (27.71)	24 (28.91)
	No	8 (17.77)	28 (62.22)	32 (38.55)	34 (40.96)
Education of mothers	Under graduated	8 (17.77)	6 (13.33)	8 (9.63)	6 (7.22)
	Diploma/Bachelor	33 (73.33)	29 (64.44)	30 (36.14)	32 (38.55)
	Master- PhD	4 (8.88)	3 (6.66)	2 (2.40)	5 (6.02)

Table II: The descriptive total score of ACE-R based on tumor type in children with BBT and MBT

Total scores of children with brain tumors	Type of tumor	Frequency	M	SD	Standard error of mean
	MBT	45	64	17.62	3.022
	BBT	38	80	15.42	2.914

Table III: The Kruskal–Wallis test for comparison between MBT and BBT groups in the total score of ACE-R

Type of tumor	Frequency	Mean of ranking	X ²	df	P
MBT	45	25.43	39.90	1	•••••
BBT	38	49.79			

Table IV. Difference between patients with BBT and MBT in attention/orientation, memory, fluency, language, and visual-spatial abilities in ACE-R

Subscales score	Type of tumor	Mean of rankings	X ²	df	P
Attention-orientation	MBT	19.28	40.90	1	00.00
	BBT	38.44			
Memory	Short term	MBT	43.65	1	00.00
		BBT			
	Long term	MBT	38.27	1	00.00
		BBT			
Fluency	MBT	27.49	36.79	1	00.00
	BBT	51.14			
Language	MBT	31.12	31.42	1	00.00
	BBT	45.20			
Spatial-visual ability	MBT	15.14	24.84	1	0.5
	BBT	28.13			

Discussion

The aim of this study was to compare children with BBT and MBT in terms of cognitive impairment. The findings showed a significant difference between two groups of patients regarding attention/orientation, memory, fluency, language, and visual-spatial abilities. The previous studies rarely focus on differences between the patients with MBT and BBT in psychological differences. In a study, Hickmann et al., (27) compared the psychological consequences of BBT and MBT in adults. They showed that although the patients with BBT were less considered, they suffered from depression and suicidal thoughts, like patients with MBT. In a parent's and teachers' reports, Gallu et al., demonstrated that children with cerebral MBT showed more difficulties in academic, cognitive, and motor functions compared to BBT group. They also revealed that both motor and cognitive impairments were found to be associated with the extension of the lesion

to the dentate nuclei in both of groups. The aforementioned study emphasized that both groups experienced motor and cognitive impairments and needed interventions (28). Tucha et al., (29) studied cognitive damage in patients with a brain tumor before their treatment. They found that the patients suffered from CI even before treatment. This result is in line with the findings of this study. Other research concentrated on the side-effects of treatments such as surgery, radiotherapy, and chemotherapy. For example, Brown et al., (30) showed that regular treatments negatively affected the patients' cognitive abilities. For example, surgery by destroying the tissues, affects the function of the demolished area. In a study carried out in Japan, the researchers after 2 years of follow-up found out that children with tumors showed a 10% reduction in IQ compared with the basic level. This injury was significantly more serious in younger children (31). One of the limitations of this research was that the

age of children and the rate of vulnerability, compared to age, was not studied. The findings of this research are in line with Schmahmann's syndrome or cerebellar cognitive affective syndrome (CCAS). Schmahmann (32) indicated that patients with injury in cerebellum had problem in 3 areas of executive functions (abstract thinking, working memory, and problem-solving), language (aphasia, apraxia, and dyslexia) -metalinguage (ambiguity, sarcasm, proverb, and grammar), and spatial cognition (memory and visual-spatial cognition). The Addenbrooke's test was applied for all the 3 areas and the results represented that both groups (BBT and MBT) had a problem in all the 3 areas. The cognitive dissonance theory states that as the cerebellum coordinates the speed, repetition, rhythm, power, and accuracy of activity in humans' movement activities, it also determines the speed, cohesion, capacity, and accuracy of the cognitive activities (33). From an evolutionary perspective, the cerebellum had been developed only for movement activities, but then, it was developed in cognitive activities by making the dentate nucleus and vermis, as well. The recent studies confirmed the function of the cerebellum in the independent attention of sensorimotor activities related to attention. Schewizer et al., (34) demonstrated the function of cerebellum in visual attention and Tavano et al., (35) revealed the role of cerebellum in spatial attention. Cerebellum is of special importance in language and many studies proved this point experimentally. The cerebellum affects the quality of verbal working memory, the fluency of speech, reading, and speaking (36). Another effect of cerebellum, which has been determined on language and speech, is "silent cerebellar" syndrome. Many children after removing the tumor from their cerebellum fall completely in silence and are not able to talk for a short time. In most cases, this problem gets resolved, but they still speak with

stammering. Their speech gets slower and their intonation is not changed and they get apraxia of speech. The syndrome can be the result of damage to the posterior part of cerebellum, brainstem, and ischemia in these areas that may be due to operation or tumor. By the way, in the present research, none of the patients suffered from silent cerebellar syndrome. The intensity of the cognitive problems determines the need for early rehabilitation. The defect in the function of the children diagnosed with brain tumors may last a long time even after treatment. Being aware of the severity of the injury can help manage these conditions in the early stages of the injury by applying proper instrument for evaluating cognitive damage ratio matters in such situations. The instrument is required to have proper characteristics. At first, it must be precise and simple in order to investigate cognitive defects. The patients, who have brain damage, may not be able to handle the cognitively complicated tasks; therefore, it calls the accuracy of evaluation into question. If the evaluation is going to be performed at the hospital and during the period of treatment, the tasks must be simple and short so that the patient can do them. Therefore, Addenbrooke's test seems suitable for the assessment of cognitive impairment in hospital. In the past, the cognitive and behavioral problems of the children with brain tumor were investigated through reports of parents and teachers (37), and the real function of the children was less studied. Although mothers may show a high sensitivity to the cognitive changes of their children, they may have a bias in this evaluation, having hyper-optimism or hyper-criticism view towards their children, that can lead to errors in assessment; while the instruments that study the cognitive problems in children directly, are more accurate than parents' report. The instruments related to brain imaging have some problems. These instruments determine which areas of the brain are dealing with a disability in doing

cognitive tasks. These studies are valuable, but they have some limitations. Brain imaging instruments are both costly and time-consuming. The cognitive damage or disability in doing specific tasks may not be related only to the tissue damage but may be related to the synapse interactions. Sometimes, the tissue may be damaged, but the cognitive function remains flawlessly because other parts of the brain compensate for it. Applying tasks-based instruments such as Addenbrooke's test can cover these limitations. The other achievement of this research was a comparison between two groups of children with MBT and BBT. The children with MBT showed a worse function in all aspects compared with the children with BBT, while the type of the treatment and the area of the brain damage were controlled in both of the groups. This difference can be due to the offensive nature of the cancerous tumors. It seems that, in addition to mechanical pressure, the tumor causes other changes in the brain. These changes are not absolutely known, but they affect the cognitive function. Postoperative complications and severe or mild hydrocephalus could also be effective. In addition to the nature of the tumor, the role of the psychosocial factors cannot be ignored. Generally, patients with BBT are ignored and less investigated. Therefore, their cognitive damages are ignored, as well. Although they are less damaged than the group of children with benign tumors, their cognitive damages are remarkable. One limitation of the study was the lack of cognitive rehabilitation protocols during the treatment process in literature. The results of this study, as well as similar studies, emphasized the cognitive and rehabilitation needs. The present study suggest cognitive rehabilitation to help children with BBT and MBT who have problems in attention, memory, language use, and spatial-visual abilities.

Conclusion

In this study, some factors affecting IC due to tumor growth in BBT and MBT children were addressed. However, it should be noted that one specific factor cannot explain impairments. The study of brain tumors showed a strong link between the physical and psychological factors, which can help oncology researchers to have a deeper understanding of tumors' nature. Recognizing the pathology of the tumor may create a new way to understand the behavioral and emotional difficulties, as well as CI. Designing a cognitive rehabilitation for children with brain tumor is suggested.

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Conflict of interest

Authors declared no conflict of interest.

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