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Cognition trajectory in Duchenne muscular dystrophy

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Abstract

Background Duchenne muscular dystrophy (DMD) is an X-linked recessive disease brought on by genetic changes that alter the dystrophin (DYS) protein. There has been growing evidence that children with DMD have been at higher risk of developing symptoms of neurodevelopmental disorders. We aimed at defining the cognitive difficulties and their categories in patients with DMD, compared to healthy controls, and assessing their relation with the functional severity. This work was a multi-center, observational, case–control study conducted on DMD patients. Age and sex-matched healthy subjects with no neurologic, psychiatric, or medical comorbidities were included as normal controls.

Results There was a statistically significant difference in cognitive patterns between the studied groups. We have observed a significant relationship between cognitive difficulties and functional severity assessment in our patients. There was a statistically significant difference between the studied cases regarding basic characteristics and correlation between cognitive functions and demographic data.

Conclusions The decline in cognitive functions in DMD patients compared to healthy controls was established. Education was the most affected domain in patients, with more speech delay and dropping out of school. Therefore, it was recommended to establish cognitive screening as a routine in the evaluation and follow-up of DMD children.

Keywords Cognition, Duchenne muscular dystrophy, Motor function

Significance statement

The results of our research bring attention to the importance of early screening and support and the need for continued follow-up of children with DMD. Special attention should be given to children with educational and cognitive difficulties, because they are more likely to receive support and health care services.

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Background

It is currently unknown how many elements of cognitive function are affected by neuromuscular disorders, even though these diseases present a wide variety of clinical symptoms [1]. Neuromuscular diseases are known to predominantly affect a patient's motor function, but they can also have significant effects on cognitive function [2]. Three large diverse groups of neuromuscular disorders that have been associated with cognitive abnormalities include motor neuron illnesses, muscular dystrophies, and mitochondrial disorders [3, 4]. Cognitive impairment is a recognized feature of around one-third of DMD patients. One early sign of this condition is delay in language or global development [5]. The dystrophin protein (DYS) is essential to the structural organization of the central nervous system (CNS). It is responsible for organizing gamma-amino butyric acid type A (GABAA) receptors, which are normally expressed at the postsynaptic

membrane in inhibitory synapses of brain areas linked to emotional and cognitive behavior, such as the cerebellum, hippocampus, amygdale, and sensory cortices [6]. Though its exact role in the nervous system is unknown, dystrophin is generally present in brain regions involved in higher order function. The dystrophin gene's protein products are far more varied in brain tissue, even though the expression of dystrophin in the brain is just 10% of that in muscles. It is made up of shorter proteins, with Dp71 being the main one expressed in the brain, and the whole protein is Dp427. The presence of Dp71 close to the perivascular astrocyte end foot suggests that it may have a role in the operation of the blood–brain barrier and the possible entrance of inflammatory substances from the peripheral nervous system into the brain. Dp427 is only found in neurons and certain brain regions in the central nervous system (CNS), such as the neocortex, cerebellar Purkinje cells, amygdale, and hippocampal areas. Dp47's interaction with DGC is essential for the formation and maintenance of new synaptic connections [2]. Furthermore, intellectual impairment has been associated with the disruption of many dystrophin isoforms, suggesting the critical need for these isoforms for appropriate brain function [7]. There is growing evidence that children with DMD are more likely than the general pediatric population to exhibit signs of neurodevelopmental problems, even though neuromuscular illnesses have a wide range of clinical presentations. Even still, little is known about how these illnesses affect different aspects of cognitive function. Cognitive impairment is a known feature of around one-third of DMD patients. One of the illness's initial symptoms may be delay in linguistic or global development [8]. Given this, the current study is aimed at describing the cognitive difficulties linked to DMD relative to healthy controls, and ascertaining the relationship between these difficulties and the functional severity in our studied patients.

Methods

Over 3 months, 40 DMD patients were recruited from the neuropsychiatry departments at Aswan university and the October 6 university hospitals for a multicenter, observational, case–control research. A group of 40 participants who were similar in age and gender and who did not exhibit any medical, mental, or neurological comorbidities were included as controls. Only male sex was studied. The Ethics Committee of our University in Egypt's Faculty of Medicine gave its approval to the protocol (IRB: 698/12/22). All participants gave their signed, informed consent after being told about the purpose and design of the study. Individuals with a clinical diagnosis of DMD, validated by genetic testing, were included. Individuals who fulfilled the study's eligibility criteria included those who were over 8 but under 18 years, as well as those whose Multiplex ligation-dependent probe amplification (MLPA) test indicated DMD gene deletion or duplication. One patient, who was not even 8 years, had normal multiplex ligation-dependent probe amplification (MLPA), was severely intellectually disabled, had respiratory embarrassment, used respiratory assistant machines, had cardiac complications, and had a medical or surgical history of any condition that may have an impact on neurocognitive functioning (such as a brain tumor or significant head injury). It was necessary to establish a minimum sample size of 80 individuals, with an error probability of 0.05% and 95% power on a two-tailed test (42 cases of DMD and 42 controls).

A single very skilled neurologist assessed each patient clinically. Age, sex, family history (for consanguineous marriage, the existence of comparable illnesses, any neuropsychiatric problems in the family, and developmental history), and a complete medical and neurological history and examination were conducted. The following scales were used to complete the motor assessment: the Medical Research Council (MRC) Scale, which has a score ranging from 0 (no contraction at all) to 5 (normal), is one tool used to quantify motor function severity and progression [9]. Another tool is the Motor Function Quantify Test (MFM-32). The range of a total score is 0–96 [10]. The third tool is the 17-item North Star Ambulatory Assessment (NSAA) rating scale, which has a 0–2 rating range. A total score of 0 indicates total non-ambulation, whereas a score of 34 indicates full independence [11]. The Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), which is a standardized test that yields a full-scale intelligence quotient (FSIQ), or overall intellectual ability, and index scores that measure various domains, such as verbal intelligence, non-verbal intelligence, working memory, and processing speed, was used to conduct cognitive assessment. These instruments are widely recognized as reference points for developmental and cognitive assessment in developmental age [12]. The verbal comprehension index (VCI), processing speed index (PSI), working memory index (WMI), and perceptual reasoning index (PRI) are the sub-indices of the WISC-IV. The Benton Visual Retention Test (BVRT) is a test that evaluates visual memory and perception, and is given one at a time [13]. The corresponding author alone was in charge of the data and has unrestricted access thereto.

The computer was given data, and IBM SPSS software package version 20.0 was used for analysis. (IBM Corp., Armonk, NY, USA) numbers and percentages were used to describe the qualitative data. The distribution's normality was confirmed using the Kolmogorov–Smirnov test. The terms range (minimum and maximum), mean,

standard deviation, median, and interquartile range (IQR) were used to characterize quantitative data. The results were deemed significant at the 5% level. The Chi-square test was used to compare several groups based on categorical characteristics. For regularly distributed quantitative variables, the student *T* test was employed to compare the two groups under study. For group correlations, Spearman's rank correlation coefficient was employed. Based on the examination of the ROC curves, the optimal cutoff was determined by determining the biomarker value that yielded the best combination of sensitivity and specificity, or the value that maximized the sum of the sensitivity and specificity. The Youden index was used to conduct the ROC curve study.

Results

Table 1 displays the basic characteristics of the DMD patients under study.

We have found high statistically significant differences in cognitive patterns between the examined groups, as displayed in Table 2 and Fig. 1.

Table 3 demonstrates the lack of association between demographic information and cognitive skills. The cognitive patterns (measured by Wechsler scales, BVRT accurate, and full-scale intelligence) and motor assessment scales (MRC, MFM32, and NSAA) displayed a strong positive link in the patients under study.

Table 4 illustrates the strong negative associations between BVRT error and motor assessment scores.

Table 5 and Fig. 2 demonstrate that, an AUC of 1, degree of sensitivity of 100%, specificity of 100%, the cutoffs for VCI, WMI, and FSIQ at 101.5, 96.5, and 101, respectively, could be used to differentiate between cases and controls.

Table 1 Basic characteristics of studied patients with DMD

Parameter	DMD ($n=40$)	*p* value
Age (mean ± SD, range)	11.45 ± 2.49 (8–15)	
Age at onset (mean ± SD, range)	2.33 ± 0.47 (2–3)	
Duration of disease (mean ± SD, Range)	9.13 ± 2.43 (5–13)	
Wheelchair dependence (n; %)		
Permanent	18 (45%)	
Intermittent	9 (22.5%)	
Never	13 (32.5%)	
Education of patients (n; %)		
Regular	8 (20)	< 0.001*
Special	32 (80)	
Education of mother (n; %)		
Low	7 (17.5)	0.603
Moderate	13 (32.5)	
High	20 (50)	
Education of father (n; %)		
Low	2 (5)	0.201
Moderate	13 (32.5)	
High	25 (62.5)	
Family history for neurological diseases (n; %)		
Negative	29 (62.5)	< 0.001*
Positive	11 (27.5)	
Medication use (n; %)		
Steroids	38 (95)	
Stimulants	2 (5)	
Functional assessment		
MRC scale (mean ± SD, range)	3.9 ± 1.28 (1–5)	
MFM-32 (mean ± SD, range)	65.13 ± 26.22 (8–96)	
NSAA (mean ± SD, range)	23.15 ± 8.69 (2–34)	

The Chi-square test and student *t* test were used

MRC Medical Research Council Scale, *MFM-32* Motor Function Measure Test, *NSAA* North Star Ambulatory Assessment

The *p* value: used for comparing between studied groups, *SD* Standard deviation

*Statistically significant at $p \leq 0.05$

Discussion

Duchenne muscular dystrophy (DMD), one of the most prevalent genetic diseases, affects around 1 in 3600–6000 live male births. Non-progressive cognitive deficits and slow muscular degeneration are the condition's hallmarks. Brain comorbidities may affect a person with DMD's family more severely than mobility. Moreover, DYS is essential for the central nervous system's structural organization [8].

Nearly, half of DMD patients were chronically wheelchair dependent, according to Bendixen and colleagues who reported substantially lower engagement levels in physical activities in DMD, demonstrating that growing muscle degradation is a feature of the condition [14].

A unique pattern of schooling was more prominent among our patients, according to Sayed and colleagues, who found a statistically significant difference regarding school attendance, where home-schooling and stopping school were visible in the DMD boys [6]. On the other hand, 94.7% of boys with DMD attended school, according to López–Hernández's study. The fact that our domestic educational institutions are unprepared to meet the demands of students with this kind of handicap might help to explain this [15]. Interestingly, we found a sizable proportion of DMD patients with a positive family history of neurological conditions. These results are in line with those of Sayed and colleagues who reported cases of distinct paternal consanguinity [6].

We demonstrated that our patients had significantly lower scores on the WISC-IV Scales (VCI, PRI, WMI, and PSI), BVRT, and full-scale intelligence quotient (FSIQ) than did the controls, indicating inferior cognitive functioning in DMD compared to the general population. Our results concurred with those of D'Alessandro et al. [5]. Furthermore, Chieffo and his colleagues discovered

Table 2 Cognitive patterns of the studied cases and controls

Cognitive scales	DMD ($n=40$)	Control ($n=40$)	p value
VCI (mean ± SD, range)	77.5 ± 7.12 (66–90)	119.05 ± 4.07 (113–125)	< 0.001*
PRI (mean ± SD, range)	81.55 ± 8.39 (70–97)	110.98 ± 9.88 (95–125)	< 0.001*
WMI (mean ± SD, range)	79.2 ± 8.85 (66–96)	107.3 ± 6.08 (97–119)	< 0.001*
PSI (mean ± SD, range)	81.93 ± 12.93(63–104)	102.38 ± 4.09(97–109)	< 0.001*
BVRT correct (mean ± SD, range)	3.85 ± 1.19 (2–6)	6.6 ± 0.5 (6–7)	< 0.001*
BVRT error (mean ± SD, range)	9.15 ± 1.19 (7–11)	6.4 ± 0.5 (6–7)	< 0.001*
FSIQ (mean ± SD, range)	77.83 ± 10.57 (58–95)	113.85 ± 3.76 (107–120)	< 0.001*

SD standard deviation, *VCI* verbal comprehension index, *PRI* perceptual reasoning index, *WMI* working memory index, *PSI* processing speed index, *BVRT* Benton Visual Retention Test, *FSIQ* Full-Scale Intelligence Quotient, *t* Student *t* test, *VCI* verbal comprehension index, *PRI* perceptual reasoning index, *WMI* working memory index, *PSI* processing speed index, *BVRT* Benton Visual Retention Test, *FSIQ* Full-scale Intelligence Quotient

p value: used for comparing between the studied groups

*Statistically significant at $p \leq 0.05$

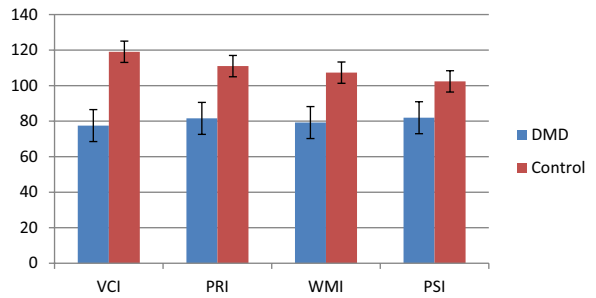

Fig. 1 Comparison between the studied cases according to, WISC-IV Scales

that IQ appeared to decrease with age and increased muscle weakness in children with DMD, who also had a substantial prevalence of mental disability [16]. Furthermore, compared to the same controls, children with DMD showed statistically significant differences in learning, executive, and memory (short- and long-term) scores [5]. Furthermore, Sayed and colleagues concentrated more on the DMD boys' comprehension of difficult problems, their capability to provide intelligent responses, their ability to take in, hold onto, and recall information, their verbal expressiveness, and their working memory [6]. Peristeri and colleagues demonstrated deficits in verbal short-term memory and fluency as well as visuospatial long-term memory [17], in addition to a loss in full-scale IQ. According to Vengalil's research, boys with DMD had noticeably lower IQs. It was discovered that the Performance IQ was higher than the Verbal IQ [18]. Since mdx mice lacked dystrophin, cytokines were found in the hippocampus. Furthermore, peripheral tissue and plasma from DMD patients exhibit these cytokines at persistently high levels. Because of their neuromodulatory effects on the hippocampus, important proinflammatory cytokines, such as IL-1, TNF-, and IL-6, have been associated with poorer memory and learning.

Table 3 Correlation between cognitive functions and demographic data in studied cases

	Age		Age at onset		Duration of illness		Education of patients		Family history of other neurological diseases	
	r	p value	r	p value	r	p value	r	p value	r	p value
VCI	− 0.097	0.394	− 0.277	0.084	− 0.149	0.359	0.178	0.272	0.076	0.643
PRI	0.044	0.700	0.096	0.557	0.150	0.356	0.033	0.839	− 0.034	0.834
WMI	− 0.112	0.324	0.021	0.899	0.020	0.901	0.033	0.840	0.056	0.730
PSI	− 0.044	0.696	0.184	0.256	0.017	0.915	− 0.155	0.341	0.267	0.096
BVRT correct	− 0.090	0.429	0.134	0.409	− 0.073	0.653	− 0.064	0.695	0.174	0.283
BVRT error	0.090	0.43	− 0.134	0.41	0.073	0.65	0.064	0.70	− 0.174	0.28
FSIQ	− 0.043	0.704	0.078	0.632	0.054	0.742	− 0.020	0.901	0.150	0.356

VCI verbal comprehension index, *PRI* perceptual reasoning index, *WMI* working memory index, *PSI* processing speed index, *BVRT* Benton Visual Retention Test, *FSIQ* Full-scale intelligence Quotient

*$p < 0.05$ was considered significant

Table 4 Correlation between cognitive functions and functional assessment

	MRC		MFM-32		NSAA	
	r	*p* value	*r*	*p* value	*r*	*p* value
VCI	0.481**	0.000	0.474**	0.000	0.488**	0.000
PRI	0.451**	0.000	0.452**	0.000	0.459**	0.000
WMI	0.485**	0.000	0.474**	0.000	0.470**	0.000
PSI	0.258*	0.021	0.238*	0.033	0.277*	0.013
BVRT correct	0.399**	0.000	0.385**	0.000	0.384**	0.000
BVRT error	− 0.399**	0.00	− 0.385**	0.00	−0.384* *	0.00
FSIQ	0.457**	0.000	0.443**	0.000	0.460**	0.000

VCI verbal comprehension index, *PRI* perceptual reasoning index, *WMI* working memory index, *PSI* processing speed index, *BVRT* Benton Visual Retention Test, *FSIQ* Full-scale Intelligence Quotient, *MRC* Medical Research Council, *MFM-32* Motor Function Measure Test, *NSAA* North Star Ambulatory Assessment

*$p < 0.05$ was considered significant **$p < 0.005$ was considered significant

Table 5 ROC curve analysis for the use of cognitive functions to discriminate between cases and controls

	AUC	*p* value	95% C.I		Cut off[a]	Sensitivity	Specificity
			L.L	U.L			
VCI	1.0	< 0.001*	1.0	1.0	**101.5**	100.0	100.0
PRI	0.997	0.003*	0.991	1.0	**97.5**	95.0	100.0
WMI	1.0	< 0.001*	1.0	1.0	**96.5**	100.0	100.0
PSI	0.915	0.032*	0.853	0.997	**96.5**	100.0	80.0
BVRT Correct	0.980	0.012*	0.956	1.0	**5.5**	100.0	90.0
FSIQ	1.0	< 0.001*	1.0	1.0	**101**	100.0	100.0

Bold values indicate significant cognitive disturbances that discriminate between cases and controls

AUC area under a curve, *VCI* verbal comprehension index, *PRI* perceptual reasoning index, *WMI* working memory index, *PSI* processing speed index, *BVRT* Benton Visual Retention Test, *FSIQ* Full-scale intelligence Quotient, *CI* Confidence Intervals

[a] Cut off was chosen according to Youden index

*Statistically significant at $p \leq 0.05$

Thus, there may be a neuroimmune component to the CNS dysfunction in those with dystrophin deficiency [19]. While performance IQ is less compromised, DMD patients often exhibit a cognitive profile with abnormalities, particularly in the areas of verbal working memory and auditory comprehension [18]. Reports state that up to 40% of DMD patients have difficulty with reading. Further evaluations revealed that these individuals also had problems with phonological awareness/processing and short-term verbal memory [18].

The severity of our DMD patients' motor function as determined by the MRC, MFM32, and NSAA was significantly correlated with their cognitive function as determined by the Wechsler scales, BVRT correct, and full-scale intelligence. This suggests that as their muscle weakness worsened, their cognitive function appeared to be deteriorating. The results of Doorenweerd [20] observed that children with DMD who experience motor delay and delayed language milestones in their early years of life will do badly on intelligence tests beyond the age of four and will have a greater degree of cognitive impairment were supporting these findings. Notably, walking delay and cognitive impairment were found to be strongly correlated by Mirski and colleagues if cognitive development was delayed, boys with DMD were three times more likely to have a walking delay [21]. Furthermore, the results of D'Alessandro and colleagues demonstrated a strong association between the overall scores on the North Star Ambulatory Assessment (NSAA) and the WISC-IV FSIQ scores [5].

The main pathophysiological mechanisms causing cognitive impairments in DMD include the involvement of dystrophin in embryonic development, the interaction between genes and non-genetic agents, and the existence of numerous dystrophin isoforms [22]. Several biochemical mechanisms have been linked to the loss of muscle mass (muscle atrophy) and cognitive impairment [23]. These mechanisms include altered myokine synthesis, oxidative stress, inflammation, insulin resistance, aberrant protein buildup, and mitochondrial dysfunction.

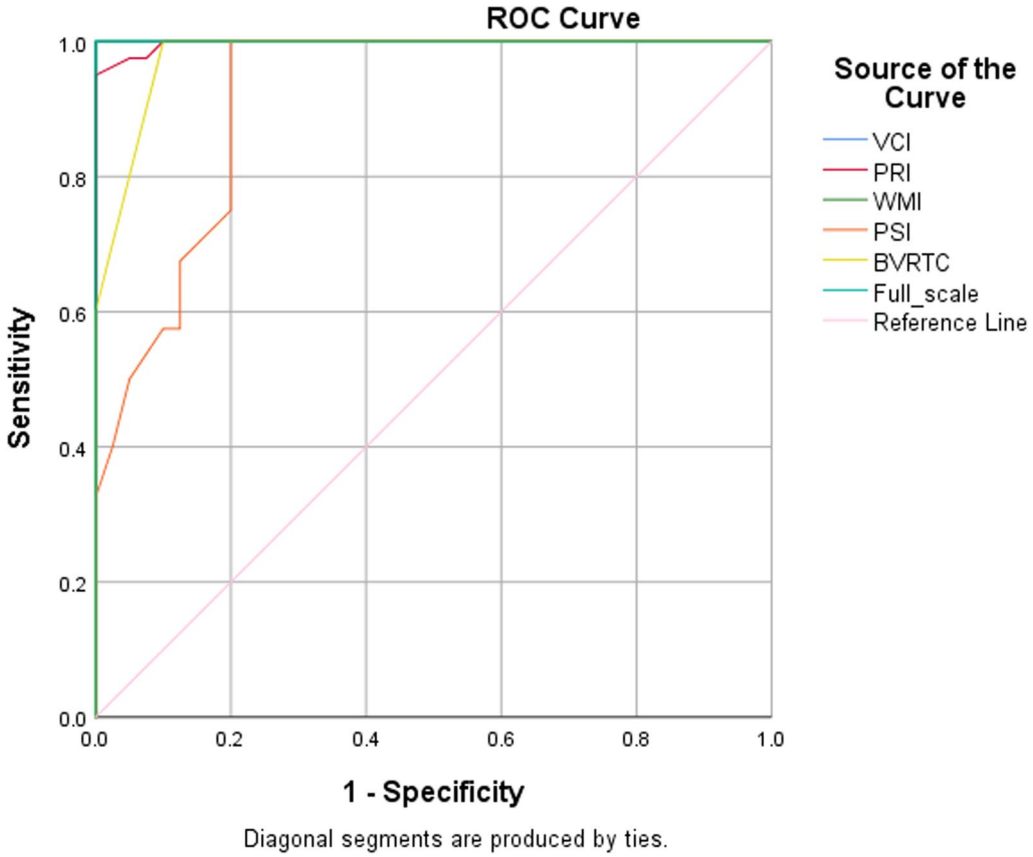

Fig. 2 ROC curve analysis for the use of cognitive functions to discriminate between cases and control. *VCI* verbal comprehension index, *PRI* perceptual reasoning index, *WMI* working memory index, *PSI* processing speed index, *BVRT* Benton Visual Retention Test, *FSIQ* Full-scale intelligence Quotient

Other research has considered the relationship between speech and language ability in DMD patients and cerebellar involvement. Kreis and colleagues reported that a metabolic examination of the patients' cerebellum and temporal–parietal area, which were associated with verbal IQ and short-term memory, showed severe abnormalities in glutamate and N-acetyl compounds in addition to continuous choline deficits. Many brain illnesses are associated with elevated levels of choline-containing substances, which is probably indicative of an unstable increase in membrane turnover caused by either inflammation or quicker cell division. However, the hypothesis that membrane turnover has changed is called into question by the fact that the concentration of choline molecules is consistently increased in DMD [24].

Using ROC analysis, the WISC-IV Scales (VCI, WMI, and FSIQ) were able to differentiate between patients and controls with a high sensitivity of 100% and a specificity of 100% with cutoffs of 101.5, 96.5, and 101, respectively. The WISC-IV score for DMD diagnosis shows a ROC curve with 82% sensitivity, 74% specificity, and 78% accuracy, according to Nardes and colleagues [25].

Conclusion

We have concluded that DMD patients have had worse cognitive and motor functioning, and higher rates of school dropouts than the general population. Therefore, we advise using cognitive screening as a routine component of diagnosing and treating children with DMD. If cognitive deficits are correctly identified and treated, patients with DMD may engage with caretakers more successfully, which might improve care and raise quality of life (QOL).

Abbreviations

DMD	Duchenne muscular dystrophy
DYS	Dystrophin protein
DGC	Dystrophin–glycoprotein complex
CNS	Central nervous system
MLPA	Multiplex ligation-dependent probe amplification
MRC	Medical Research Council
MFM-32	Motor Function Measure
NSAA	North Star Ambulatory Assessment
WISC-IV	Wechsler Intelligence Scale for Children, Fourth Edition
FSIQ	Full-scale intelligence Quotient
VCI	Verbal comprehension index
PRI	Perceptual reasoning index
WMI	Working memory index
PSI	Processing speed index
BVRT	Benton Visual Retention Test

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Author contributions
T AA did the acquisition, analysis, interpretation of data and as well as contributing with most of the writing and review of the manuscript. A SH applied the cognitive tests used. A S did the acquisition of cases. K RM did the analysis, and review it. All authors read, agreed and approved the final manuscript.

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Availability of data and materials
The corresponding author takes full responsibility for the data, has full access to all of the data, and has the right to publish any and all data separate and apart from any sponsor. This statement was mentioned in the methods section of the research.

Declarations

Ethics approval and consent for publication
The Institutional Ethics Committee, Faculty of Medicine, Aswan University granted approval for the study (IRB: Asw. U./698/12/22). The goals, procedures, and risk/benefit analysis of the research were fully disclosed to all patient parents. Written permission was obtained from each subject's parents or legal guardian upon admission to the research, in the event that parents were unable to participate. The Declaration of Helsinki was followed in conducting the study.

Consent for publication
Not applicable.

Competing of interests
The authors declare that they have no competing interests.

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Publisher's Note

Abeer A. Tony did the acquisition, analysis, interpretation of data and as well as contributing with most of the writing and review of the manuscript.

Sarah Abdelrashid did the acquisition of cases.

Hoda S Ahmed applied the cognitive tests used.

Mohamed Rizk Khodair did the analysis, and review it.