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Corpus Callosum Tractography and its Correlation with Cognitive and Behavioural Changes in Children with Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Background: Very few studies have investigated the changes in white mater, corpus callosum (CC) specifically, in attention-deficit/hyperactivity disorder (ADHD) patients and its relation to cognitive and behavioral changes in ADHD patients. This study aimed to investigate the correlation between tractography of CC, behavioral and cognitive changes in ADHD patients. **Objectives:** To detect any morphological changes in corpus callosum in patients with attention-deficit/hyperactivity disorder through diffusion tensor image (tractography) and to elucidate its relation with cognitive and behavioral changes of patients with ADHD.

Patients and Methods: A case-control study was done on 100 children divided into two groups; cases and controls at Menoufia University Hospitals. They were selected according to certain inclusion and exclusion criteria. Diffusion tensor imaging (DTI) of CC was done to both groups. Both behavioral and cognitive functions were assessed in correlation with radiological data.

Results: There were no significant differences between the groups regarding demographic data that included age and sex, while statistically significant difference (p value <0.001*) was detected in IQ in ADHD (mean IQ was 89.62) compared to control (mean IQ: 96.08). The mean FA value (a measure of white matter consistency in DTI) was higher in control group than in ADHD group in all subdivisions of corpus callosum with no significant difference between the two groups except for the isthmus part (p value 0.034) whose fibers were originating from sensory motor cortex denoting defective functioning in mentioned areas.

Conclusion: Diffusion tensor image study of corpus callosum in attention deficit hyperactivity disorder reflected defective inter-hemispheric connectivity mainly sensory motor cortices through isthmus part of corpus callosum.

Keywords: Corpus callosum tractography, Cognitive and behavioural changes, Children, Attention-deficit/hyperactivity disorder.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder used to be named as hyperkinetic disorder (HKD) **(1)**. It is characterized by three main characteristics which are hyperactivity, impulsivity and inattention **(2)**.

Its prevalence is estimated about 5-7% of children and adolescents' population. According to DSM5, There are three subtypes of ADHD namely, predominantly inattentive, predominantly hyperactive/ impulsive and combined type **(3)**. According to DSM5, clinical diagnosis of ADHD necessitates the presence of at least 6 symptoms of hyperactivity /impulsivity and at least 6 symptoms of inattention. The high degree of heterogeneity in ADHD drags attention to the possibility of different underlying theories explaining the condition **(4)**.

With evolution of Neuro-radiological interventions, studying ADHD using structural and functional magnetic resonance imaging (MRI) started to develop recently. Imaging of the brain anatomy of ADHD has become the main stay for diagnosis **(5)**.

For a decade, most studies have focused only on frontal-striatal regions and detected smaller volume of the brain in the affected patients. As many studies approved, there is a 3% to 4% global reduction in brain volume with abnormally small caudate nuclei in ADHD patients **(6)**.

Indeed, not all patients of ADHD had cerebellar or fronto-parietal atrophy as declared. Other areas of the brain must be searched carefully according to the specific clinical presentation. This study aimed to investigate whether there is a correlation between tractography of corpus callosum, behavioral and cognitive functional changes in ADHD patients.

PATIENTS AND METHODS

This study included 100 children that were grouped into cases and controls at Menoufia University Pediatric and Child Psychiatry Outpatient Clinic.

Inclusion Criteria: Diagnosis with attention deficit and hyperactivity disorder according to the criteria of DSM 5**,** age from 3 up to 14 years, both male and female, IQ of ≥ 80.

Exclusion Criteria: Patients with co-morbid major psychiatric disorder other than ADHD e.g. mental sub-normality and schizophrenia**,** children with other neurological disorders as cerebral palsy, epilepsy or organic brain lesions, children with chronic physical

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disease as heart failure, chronic renal disease, diabetes mellitus, hypertension, chronic liver disease or cancer especially leukemia , children on any psycho-stimulant drugs or any other drugs for treating ADHD, patients with substance abuse and patients whose parents are unwilling to participate in the study or to write informed consents.

Clinical data from included subjects was recorded, full general and neurological assessment, full psychiatric examination according to DSM 5, diagnostic interview using MINI-KID to exclude comorbidity, Conner's parent rating scale for diagnosis of ADHD, cognitive assessment through IQ using Wechsler intelligence rating scale, behavioral assessment through DSM 5 diagnostic criteria for ADHD, imaging by using MRI (diffusion tensor imaging (DTI)) (using GE 1.5 Tesla ,general electric company, an American multinational conglomerate incorporated in new york city and headquarted in Boston).

Ethical considerations:

An approval of the study was obtained from Menoufia University Academic and Ethical Committee. Informed written consent was obtained from parents of all children before recruitment in the study after explaining the objectives of the work.

Statistical analysis

Data were analyzed using Statistical Package for Social Science (SPSS) version 26. (SPSS Inc, Chicago, IL, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percent. Independent sample t-test; was used when comparing between two means of normally distributed data. Probability (p-value): p-value ≤ 0.05 was considered significant, p-value > 0.05 was considered insignificant.

RESULTS

A total of 100 patients were enrolled in this study and underwent brain tractography. The age range of the study population was (3–14) years, and they were grouped into patients and controls. ADHD patients were sub-categorized into three types namely, the hyperactive impulsive type, inattentive type and the combined type. Both groups were compared regarding functional and cognitive functions and its relation with tractography where FA value was measured for all parts of corpus callosum.

There was no significant differences between the groups regarding demographic data that include age and sex, and statistically significant in IQ in ADHD group compared to control group, p < 0.001 (Table 1).

Table (1): Comparison between ADHD patients and matched controls in both sociodemographic data, including age and sex, and IQ

	ADHD group (n=50)	Control group (n=50)	Test	P-value
Age (Years)				
Mean ± SD	7.84 ± 2.32	8.56 ± 2.57	-1.47 ^{t}	0.145
Range	5 - 14	4 - 14		
Cognitive IQ				
Mean ± SD	89.62 ± 3.78	96.08 ± 3.99	-4.45 ^{t}	<0.001*
Range	78 - 97	88 - 112		
Sex				
Male n (%)	22 (44%)	26 (52%)	0.64 ^{X2}	0.423
Female n (%)	28 (56%)	24 (48%)		

^{t} T-Test ^{X2} Chi-Square test p-value < 0.05 is significant. *significance

There was no statistically significant difference between cases and controls regarding FA value in different parts of corpus callosum except for the isthmus part (Table 2).

Table (2): Average FA value in CC subdivision between study groups

		Group		T-Test	
		ADHD	Controls	t	P-value
Rostrum FA	**Mean ± SD**	0.65 ± 0.09	0.68 ± 0.01	-2.14	0.053
Genu FA	**Mean ± SD**	0.65 ± 0.04	0.73 ± 0.01	-12.95	0.062
Body FA	**Mean ± SD**	0.46 ± 0.01	0.54 ± 0.08	6.39	0.108
Isthmus FA	**Mean ± SD**	0.51 ± 0.03	0.55 ± 0.12	2.67	0.034
Splenium FA	**Mean ± SD**	0.55 ± 0.01	0.63 ± 0.02	48.78	0.042

Regarding the distribution of the different subtypes of ADHD in collected data, 40% of cases were combined, 24% of cases were attention defective mainly and 36% were hyperkinetic type (Table 3).

Table (3): Distribution of ADHD types in study group

Behavioral			
		N	%
Behavioral	Combined	20	40.00
	Attention defective mainly	12	24.00
	Hyperkinetic impulsive mainly	18	36.00
Conner's rating scale	Mean ±SD	43.920±4.159	

There is a positive correlation between FA value and age as demonstrated (Figure 1).

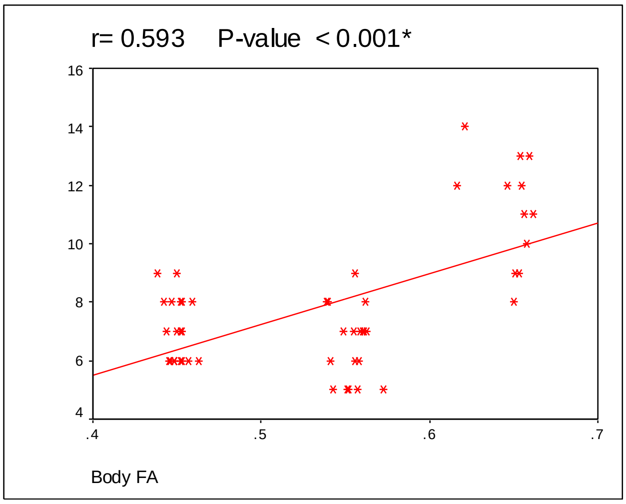

Figure (1): Correlation between age and FA value in body of CC showing positive correlation

DISCUSSION

In the current study, we compared the changes in behavioral and cognitive functions of children with ADHD with data from corpus callosum tractography dividing it into five parts by measuring FA for each.

We categorized patients into 3 categories according to DSM 5; attention deficit mainly, hyperkinetic mainly and combined comparing FA in the five parts in cases and controls after adjusting for the different variables.

Many studies measuring the area of corpus callosum found that the area of whole CC is smaller in ADHD patients compared to controls [(7)] with one study found special difference in the area of the anterior mid-body, which was reduced in ADHD patients [(8)]**.** While for DTI measures, the current study found no statistical difference in mean FA for parts of CC, which is consistent with **Ashtari *et al.*** [(9)] except for the isthmus (this difference was less pronounced for the attention defective mainly type regarding the other two types, the hyperactive mainly type and the combined one). In consistence with that a study found reduced FA at isthmus of affected patient without pointing out to its relation to behavioral and cognitive functioning [(8)].

The area of the CC tells about the inter-hemispheric connections between homologous cortical regions [(10)], which in turn means that the abnormality in the specific part of CC expresses how corresponding linked areas are affected from them such fibers originate. In other way we can tell that the studies showing reduced overall area of CC in diseased patients can reflect abnormalities in the whole cerebrum in both hemispheres. In line with that studies of structural differences of MRI in ADHD patients found that the total cortical volume is reduced by 3% to 5% in ADHD patients compared to controls [(7)]**.** Also reduced total grey and white matter has been found [(11)]**.** With one more study showing statistically significant reduction in surface area of about 7 % and cortical folding was also reduced [(12)]**.** In line with that, a study using PET scan showed that ADHD patients have decreased global cerebral glucose metabolism by 8% [(13)]**.**

Using fiber tractography, anterior mid-body of CC contains commissural fibers linking both premotor and supplementary motor cortical areas [(14)]. Also patients with ADHD were showed to have lower FA in right premotor region [(9)]**.**

In same way, the isthmus was found to harbor fibers linking the sensory-motor cortical areas, including (precentral gyrus, paracentral gyrus and post central gyrus). As was recovered in our study, fiber tractography of isthmus showed reduced FA. It was also recovered that this region is involved in trans-callosal inhibition [(15)]**.** In similar way, was also found to have significant negative effect as regarding externalizing symptoms in people with high risk for alcohol dependence [(15)].

On the other hand, the sensory-motor cortex was found to have structural and functional abnormalities in ADHD patients in measures such as cortical thickness especially the left precentral gyrus [(16)]. The above studies support the finding that the isthmus is underdeveloped in ADHD patients and gives evidence for parallel structural and functional abnormalities in related cortical regions.

Another thing to denote is the interhemispheric connectivity defect reflected in both micro and macro-structural level. In isthmus state, this could be the number, density and diameter of axons, integrity and thickness of myelin sheath, also may be the number or size of other non-axonal tissue as glia, neurons and blood vessels [(17)].

LIMITATIONS

This study had several limitations; first, the sample size was relatively small. Moreover, un-neglectable portion of patients fulfilled the criteria for ODD comorbid with ADHD. Also, the subtests of cognitive functions were not analyzed in detail; a thorough analysis of sub-cognitive tests is advisable for further analysis.

CONCLUSION

CC tractography is a relatively recent magnetic resonance mode measuring white mater defect. The study showed that DTI of CC in ADHD patients can be used as an indirect evidence of sensory–motor cortical defects in ADHD patients through defective FA value of the isthmus part of CC.

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