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Fiber Tractography and Diffusion Tensor Imaging in Children with Agenesis and Dysgenesis of Corpus Callosum: A Clinico-Radiological Correlation

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Abstract

Background

Corpus callosum is the largest commissure in human brain. It consists of tightly packed white matter tracts connecting the two cerebral hemispheres. In this study we aimed to evaluate role of fiber tractography (FT), and diffusion tensor imaging (DTI) in pediatric patients with corpus callosum anomalies and correlate findings with clinical presentation.

Materials and Methods

This prospective study included 115 children with clinical presentations and CT findings suggested corpus callosum anomalies. Their ages ranged between 2 and 12 year-old. They referred from Pediatric Neurology unit to Radiology Department in Minia University hospital for children, Minia (Egypt) from April 2018 till December 2018. They underwent MRI fiber tractography and diffusion tensor imaging after approval of ethical committee of our institution and informed consent form patients' parents.

Results

Our study included 42 (36.5 %) males and 73 (63.5 %) females. They were reviewed for corpus callosum anomalies according to Hanna classification, the commonest was hypoplasia without dysplasia 37/115 (32 %). Using DTI and FT, corpus callosum fiber defects were classified into fronto-rostral, caudal and whole body defect. Significant statistical correlation was found between ADHD, autism and loss of fronto-rostral fibers. Epilepsy and developmental delay were correlated to whole body defect and caudal fiber tract defects.

Conclusion

Based on the results, Fiber tractography and diffusion tensor imaging are newly developed promising techniques. They proved high accuracy in localization of exact affected corpus callosum white matter tract. They help to predict prognosis of patients that could not be explained by morphological changes seen in conventional MRI.

Key Words: Children, Diffusion tensor imaging, Agenesis of Corpus Callosum.

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1- INTRODUCTION

Corpus callosum is the largest commissure in the human brain. It consists of tightly packed white matter tracts connecting the two cerebral hemispheres. It has characteristic appearance on magnetic resonance imaging (1). Agenesis of Corpus Callosum (ACC) has long been a mysterious condition with many questions and very few answers. Corpus callosum allows for transfer and integration of sensory, motor, and cognitive information. It represents approximately 2–3% of all cortical fibers. For this reason, it is the largest fiber tract in the central nervous system (2, 3).

Formation of corpus callosum depends on a series of complex, highly regulated developmental events that begin during gestation and continue until adulthood. It begins at the 6th week of gestation, where axons are destined to cross the midline and grow medially to be completed at the 20th week of gestation (3, 4). Agenesis of corpus callosum is one of the most frequent brain malformations. The prevalence in children with developmental malformations reaches 230 in 10,000. It is a heterogeneous condition, which can be seen isolated or in association with other congenital syndromes (1, 5).

ACC display a wide range of morphological architecture changes. Corpus callosum is divided into three classes: Complete agenesis (CAG) when lacking all fibers, partial agenesis when absence of some fibers is noted and hypoplastic when it is thin but segments are intact. This three classification system fails to capture the wide range of morphological variability of corpus callosal morphologies (6). Abnormal white matter tracts might serve as a structural marker for altered neurodevelopment. Tractography of the corpus callosum and corticospinal tracts derived from diffusion tensor imaging (DTI) data is a promising newly developed technique that has recently been used as a predictive method for evaluation of the integrity of these tracts (7). We aimed to identify and describe changes in corpus callosal fibers concerning the morphology, microstructure and associated white matter changes using diffusion tensor imaging and fiber tractography and correlate them with clinical data.

2- MATERIALS AND METHODS

2.1 Study design and population

Our study is a prospective study which included 115 consecutive patients with clinical presentation and previous CT studies suggesting callosal anomalies. They were 76 males and 39 females. Their ages ranged between 2 and 12 years old. They all referred from pediatric neurology unit to MRI unit at radiology department, Minia University hospital for children, Minia, Egypt, in the period between April 2018 and December 2018.

2-2. Ethical consideration

All cohort patients were included after approval of ethical committee of our institution. Parents of the recruited children have signed a written informed consent before MRI examination and before anesthesia.

2-3. Inclusion and exclusion criteria

Inclusion criteria: Patients with neurodevelopmental problems and patients with CT study suggesting corpus callosum anomalies. Exclusion criteria: patients with contraindication to anesthesia as most of our patients undergo light anesthesia before MRI examination. Patients with general contraindication for MRI.

2-4. Methods

All patients recruited in the study were referred from pediatric neurology unit in Minia University hospital for children, Egypt. All patients were clinically assessed by parental interviewing, history taking

and a comprehensive clinical examination with special emphasis on neuro-developmental evaluation. Psychometric assessment was done using specialized diagnostic tools including (accredited Arabic translated forms) for childhood autism rating scale (CARS) as a tool for ASD diagnoses for children with possible autism. Relevant DSM-IV diagnostic test for ADHD was used for children with possible ADHD. The Stanford-Binet version 5.0 was our measure of cognitive assessment. Phoniatric, ophthalmic and hearing assessments were conducted for selected children with relevant clinical problems. EEG was done for all patients using Anihon Khoden 8- channel conventional EEG machine. 10- 20 international system of electrode placement and different montages were used for diagnosing epilepsy. All cohort patients were referred to MRI unit for complete MRI examination for the brain.

Patient preparation

Before MRI examination, all patients' parents were routinely questioned about any contraindications for MRI examination such as metallic prosthesis or implants. Patients' parents were asked about any condition to contraindicate anesthesia in patients that need anesthesia. An experienced consultant of anesthesia (A.H.) performed all the anesthetic procedures using IV anesthetic material (Ketamine 1-2 mg/Kg or Propofol 0.5% 1-2 mg /kg), after complete fasting of the children for at least 6 h before the procedure.

MRI technique

MRI examination was performed for all patients using a 1.5 T Ingnia (Philips Medical Systems, Netherlands), in supine position. Images were acquired in the axial, coronal, and sagittal planes using head coil. A multi planner fast field echo (FFE) localizer was used upon which the remaining pulse sequences were planned (localizing scan). MRI protocol for imaging the brain included: axial and coronal T2WI (TR 3200, TE 90, FOV 25, slice thickness 3 mm, gap 1–2 mm, NSA 3 and matrix 304 × 512); Sagittal T1WI (TR 2700, TE 108, FOV 19, slice thickness 3 mm, gap 0.5 mm NSA 3 and matrix 304 × 512); Axial FLAIR (TR 6750, TE 79, FOV 23, slice thickness 3 mm, gap 1–2 mm, NSA 3 and matrix 304 × 512); Single-shot spin-echo echo-planar imaging (EPI) and parallel imaging techniques to achieve motion-free DTI. The total imaging time for DTI and FT was 7 min which was added to the routine MR imaging examinations.

Acquisition of DTI

Diffusion-weighted imaging was performed by using single-shot spin-echo echo-planar imaging with a navigator echo phase correction. This study used a data matrix of 96 acquisitions, which was reconstructed to 128 over a field of view of 220 mm. The imaging sections were positioned to make the section perpendicular to the anterior commissure–posterior commissure (AC-PC) line. The section thickness was 2.3 mm without a gap (45–55 sections). Other imaging parameters were as follows: echo time = 70 msec, repetition time = 6,599–8,280 msec, number of acquisitions = two, b = 600 sec/mm^2.

Data processing

The data were processed on Philips Research Image-processing Development Environment (PRIDE) software (Philips Medical Systems), which is based on the Fiber Assignment by Continuous Tracking (FACT) method. Anisotropy was calculated by using orientation-independent fractional anisotropy (FA), and diffusion-tensor MR imaging–based color maps were created from the FA values and the three vector elements. The vector maps were assigned to red (x element, left-right), green (y, anterior-

posterior), and blue (z, superior-inferior) with a proportional intensity scale according to the FA. Three-dimensional FT was then achieved by connecting voxel to voxel with the FACT algorithm.

Anatomic Landmarks and ROI Locations

For tracking of the white matter fibers, the region of interest (ROI) method was applied. Experienced neuroradiologists with knowledge of the fiber pathways placed the single or multiple ROIs on the color maps. The plane of the ROI was varied according to the running direction of the white matter fibers (e.g., corticospinal tract on the axial views, corpus callosum on the sagittal views).

2-5. Image interpretation

All images were interpreted by two experienced radiologists with more than 10 years' experience in neuroradiology (N.E. and MI). As regards the conventional MRI we used the classification of Hanna for classifying corpus callosum anomaly into 8 groups (hypoplasia without dysplasia, dysplasia, hypoplasia with dysplasia, apple core, kinked, striped, anterior remnant, complete agenesis) (6). DTI images and fiber tractography (FT) were evaluated for segmental involvement of corpus callosum fibers as well as white matter tract fibers regarding the normal anatomy. We divide corpus callosum fiber into caudal fiber defect, fronto-rostral defect, and whole body defect.

2-6. Statistical analysis

All data were statistically described in terms of frequency and percentage when appropriate. Relationship between MRI findings and clinical data was calculated using Chi-square test for qualitative data with the significant correlation set at p-value $\leq .05$. For comparing quantitative data, Kruskal Wallis and Mann Whitney tests were performed. A probability value (p=0.005) was considered statistically significant. All statistical calculations were done using computer programs IPM SPSS software version 20.0.

3- RESULTS

Our study included 115 children, 42 (36.5 %) males and 73 (63.5 %) females. Their age ranged between 2 and 12 years-old. They have a wide variety of clinical presentations, the most common commonest clinical presentation was attention-deficit-hyperactivity disorder (ADHD) and autism, followed by developmental delay and seizures (**Table.1**). We classified the patients according to the morphology of corpus callosum according to Hanna classification into VIII classes. Class I: hypoplasia without dysplasia, Class II: dysplasia, Class III: apple core, Class IV: anterior remnant, Class V: hypoplasia with dysplasia, Class VI: striped, Class VII: kinked and class VIII: complete agenesis (AgCC). The most common class was Class I hypoplasia without dysplasia. Distribution of corpus callosal dysgenesis either isolated or in conjunction with other anomalies was recorded (**Table.2**).

Associated brain anomalies were recorded and we found that Probst bundle had the most common association with complete AgCC presenting 47% (n=54), and Cerebellar anomalies were the most common association with partial AgCC presenting 18% (n=21). Using DTI and fiber tractography we focused on fiber tracts bundles within corpus callosum and recorded its normal configuration (**Figure.1**). We classify the fiber defects into caudal fiber defect (**Figures 2-4**), fronto-rostral fiber defect (**Figure.5**), and all segments fiber defect (**Figure.6**). We also traced other white matter tract fibers including mesial region fibers tract, spinothalamic tract, presence or absence of

Probst bundles and cingulum fibers (**Table.3**). Statistical correlation between the fiber tract defect and clinical presentation was done and we found that fronto-rostral fiber tract defect showed significant relation with ADHD and autism with p-value 0.001. Also, significant relation between epilepsy and developmental delay and whole body defect and caudal fiber tract defect with p value 0.001and 0.002, respectively. Significant p- value less than 0.005 (**Table.4**).

Table-1: Baseline characteristics of patient's cohort.

Demographic data	Number (%)
Total number	115
Age, year	2-12
Female /Male	73/42
Symptoms	
Social & behavioral disorders	37 (32 %)
Developmental delay	24 (20 %)
Seizures	21 (18%)
Delayed speech	18 (15.6 %)
Mental retardation	15 (13 %)
Hypotonia/Flaccidity	11 (9.5 %)
Spasticity	7 (6 %)
Dysmorphic facies	2 (1.7%)
Visual abnormalities	1 (0.8)

More than one symptom in the same patient.

Table-2: Morphologic changes of corpus callosum according to Hanna classification.

Morphology	Total Number (%)	Isolated anomaly	Association with syndrome
Hypoplasia without dysplasia	37 (32%)	27	10
Dysplasia	25 (21%)	21	4
Hypoplasia with dysplasia	20 (17%)	18	2
Apple core	8 (7%)	6	2
Kinked	7 (6%)	6	1
Striped	2 (1.7 %)	2	0
Anterior remnant	1 (0.8%)	0	1
Complete agenesis	15 (13%)	10	5
Total	115 (100%)	90 (78.3%)	25 (21.7%)

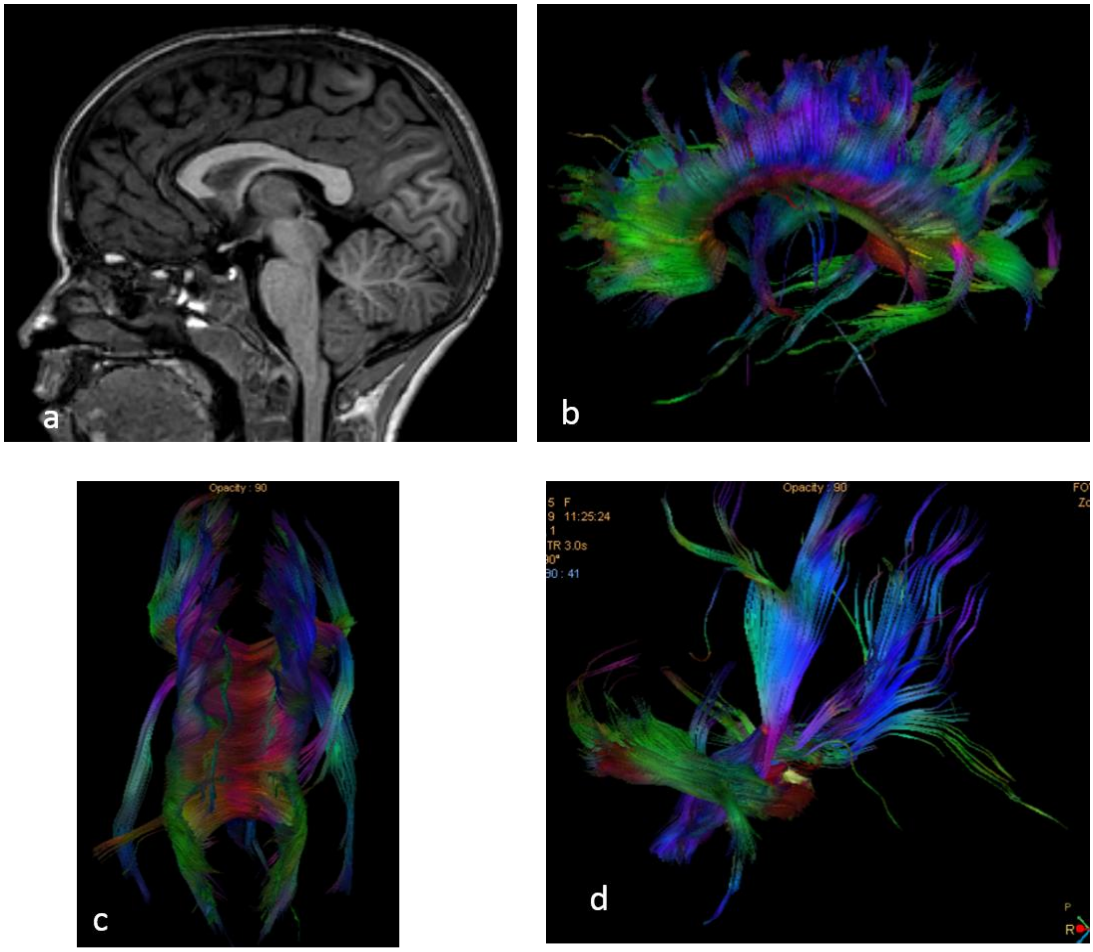

Fig.1: A 4-year- old boy with normal motor development but presented with seizures. a) Sagittal T1WI showed anatomically normal morphology of various segments of corpus callosum. b) Fiber tractography (FT) using color map axial view showed normal thickness of crossing fibers at all segments of corpus callosum. c) Sagittal view image of FT showed normal extension of the fibers at all brain areas frontal, parietal, and occipital regions as well as normal hippocampal and commissural fibers. d) Coronal oblique view showed normal corticospinal tracts.

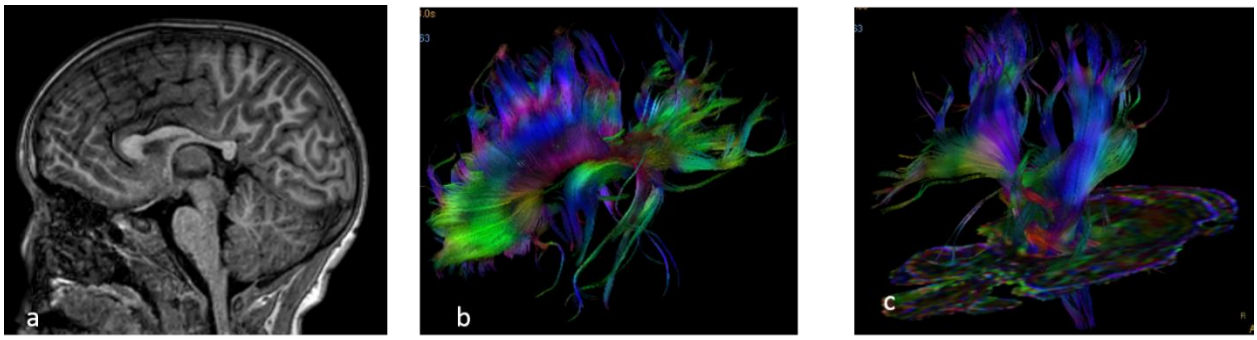

Fig.2: A 5-year-old boy presented with epilepsy but has normal motor development. a) Sagittal T1WI showed dysplastic corpus callosum with dorsal kink at the posterior segment of the body. b) Fiber tractography (FT) using color map sagittal view showed normal thickness of crossing fibers at the fronto-rostral segment and defective caudal segment at the posterior of corpus callosum. c) Coronal view image FT showed both corticospinal tracts were normal as well as normal hippocampal and commissural fibers.

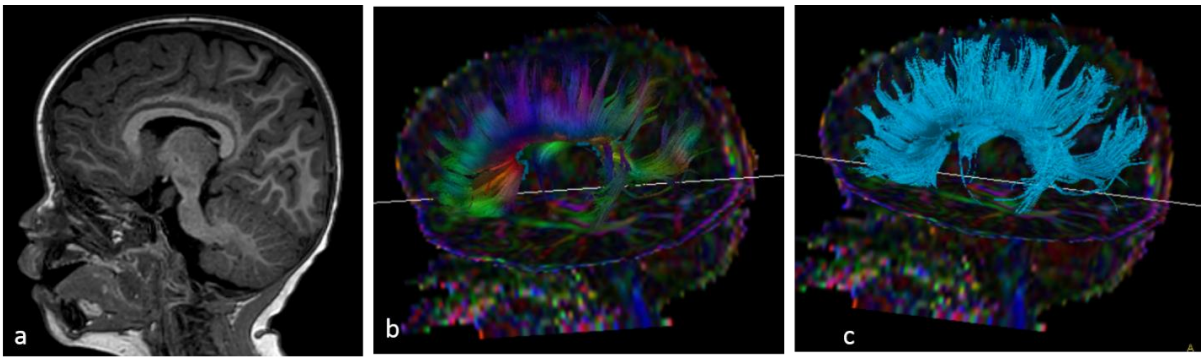

Fig.3: A 3-year-old girl with delayed motor development and visual defect. a) Sagittal T1WI showed caudal segment dysplastic corpus callosum. b) FT using color map sagittal oblique view showed segmental defect of fibers at the caudal segment of body corpus callosum with deformed anterior commissural fibers and hippocampal fibers. c) Sagittal view image of FT with blue color code showed the caudal fiber defect and deformed commissural and hippocampal fibers.

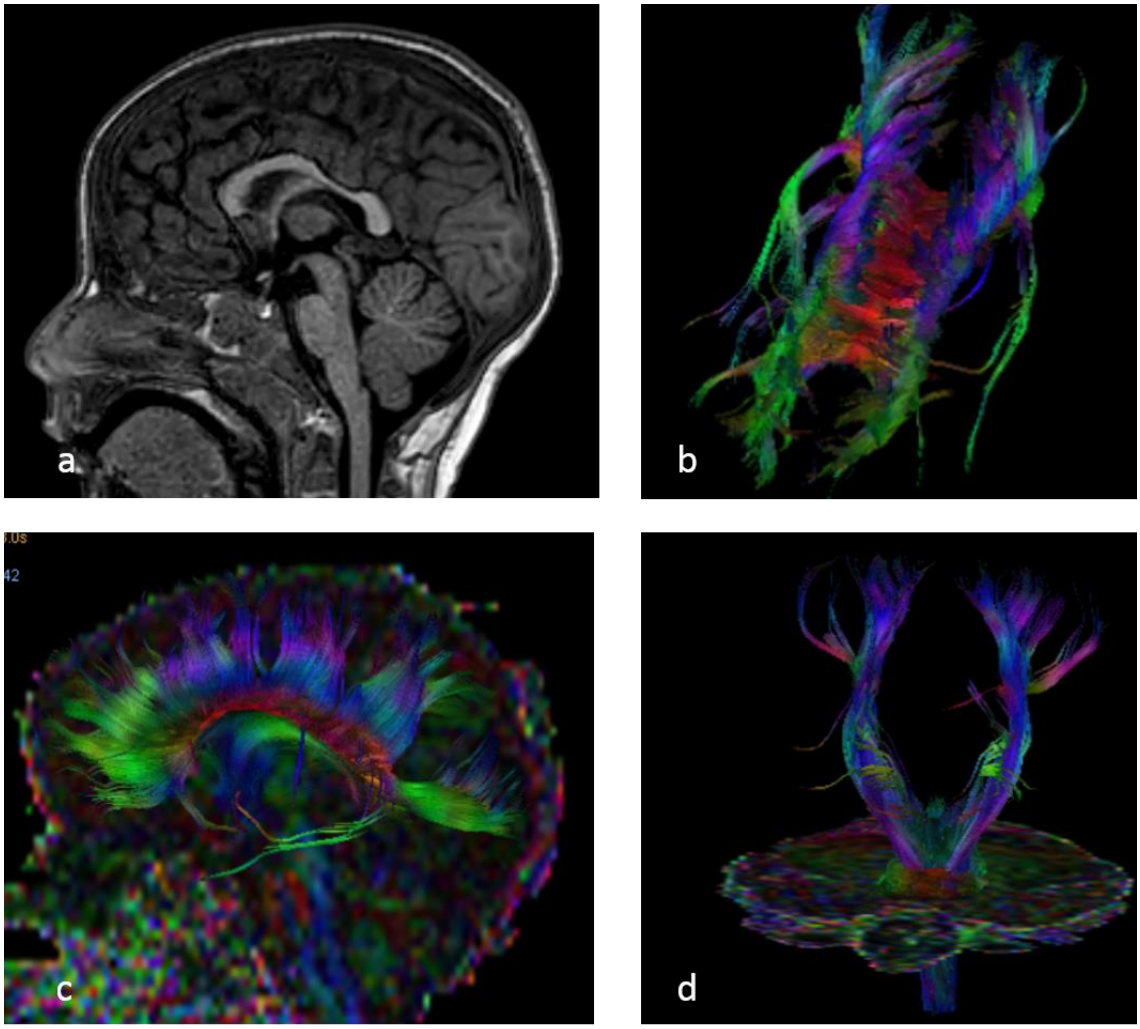

Fig.4: A 3-year-old boy with delayed motor development. a) Sagittal T1WI showed caudal segment dysplastic corpus callosum. b) FT using color map axial oblique view showed reduction of the thickness of crossing fiber. c) Sagittal view showed almost absent fibers at the caudal segment of body corpus callosum, however normal anterior commissural fibers and hippocampal fibers. d) Coronal view image of FT show normal corticospinal tracts.

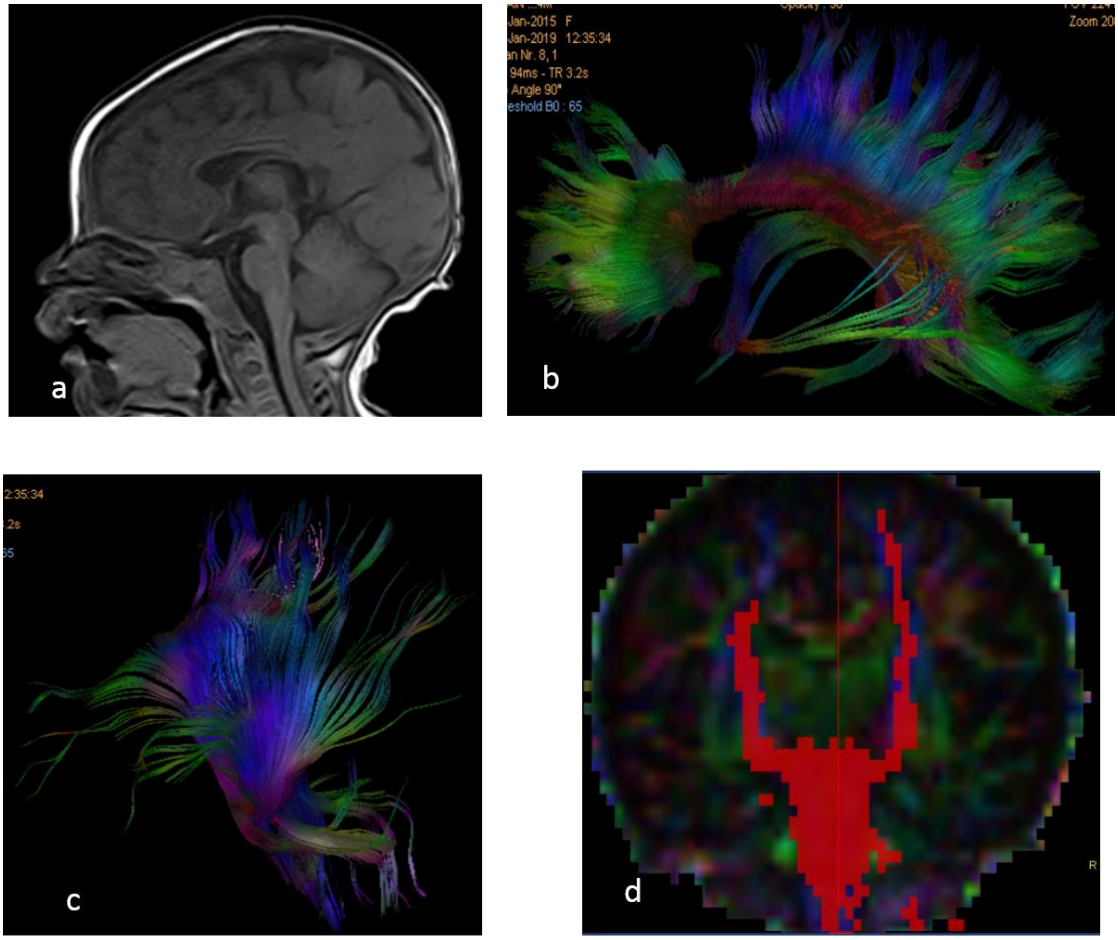

Fig.5: A 2-year-old girl presented with delayed motor development and ADHD. a) Sagittal T1WI showed hypoplastic corpus callosum. b) Sagittal view FT using color map show segmental defect at the frontal segment of body of corpus callosum and another area of defect seen at the posterior segment, however normal hippocampal and commissural fibers were noted. c) Coronal view DTI image showed defective right cortical spinal tract. d) FT sagittal oblique view showed the defective anterior fibers of the right cortico spinal tract.

Table-3: Prevalence of Associated brain anomalies in patients.

Associated anomalies	Complete AgCC n= 15	Partial AgCC or dysgenesisn=100
Brainstem anomalies	1 (6. 7%)	0 (0 %)
Cerebellar anomalies	5 (33 %)	18 (18%)
Colpocephaly	3 (20 %)	11 (11%)
Septal anomalies	2 (13%)	9 (9%)
Cysts	6 (40 %)	10 (10 %)
Cortical dysplasia	1 (6.7 %)	3 (3 %)
Migration anomalies	2 (13)	4 (4 %)
Dandy-Walker complex	2 (13 %)	8 (8 %)
Hippocampal anomalies	2 (13 %)	2 (2 %)
Probst bundles	7 (47 %)	3 (3 %)
White matter anomalies	4 (26 %)	8 (8 %)
Holoprosencephaly	1 (6.7%)	4 (4 %)
Polymicrogyria	1 (6.7%)	6 (6 %)
Chiari malformation	2 (13 %)	1 (6.7%)

AgCC: agenesis of the corpus callosum; More than one anomaly in the same patient.

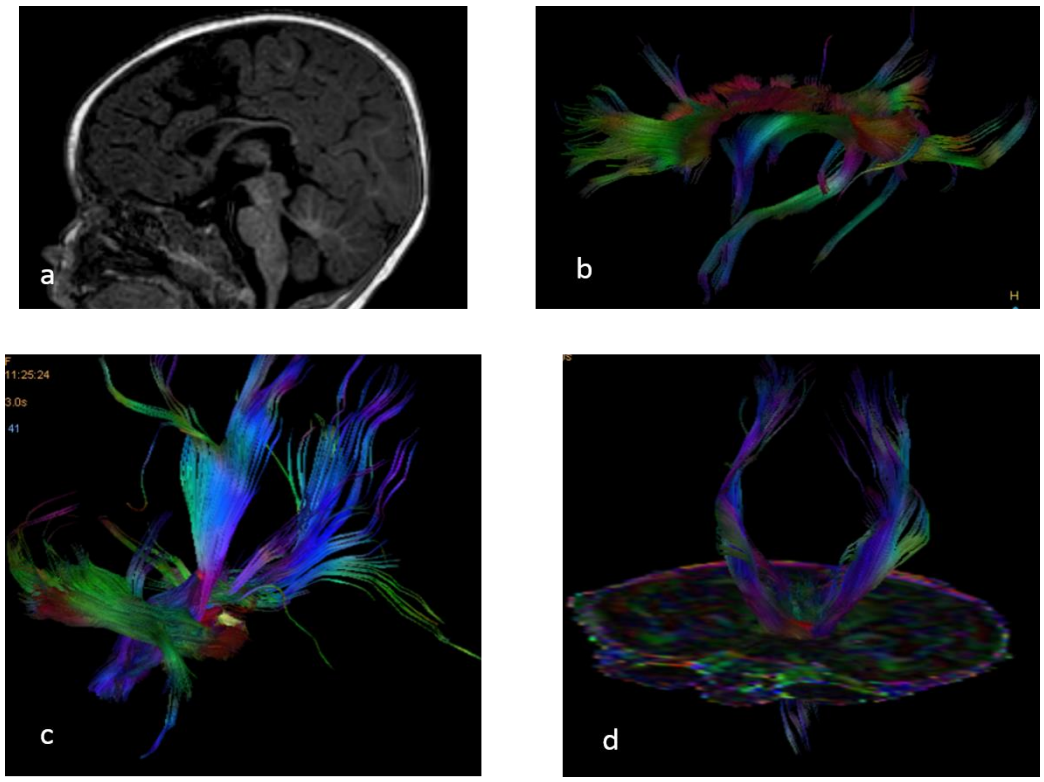

Fig.6: A 2-year-old boy with seizures. a) Sagittal T1WI showed markedly thinned out corpus callosum fibers. b) Fiber tractography (FT) using color map sagittal view showed almost complete loss of the fibers of body of corpus callosum, only small frontal fibers are seen at the area of the genu. C. d) Coronal and coronal oblique FT show normal cortico spinal tract at both sides, hippocampal, commissural fibers and cerebellar connection.

Table-4: Fiber tractography findings and segmental callosal defects and its relation to clinical presentations.

Symptom	Whole body fiber loss	Fronto-rostral fiber loss	Caudal fiber loss	P- value
Social and behavioral	-	+	-	< 0.001
disorders	+	-	+	< 0.002
Developmental delay	+	-	+	< 0.001
Seizures	+	-	-	< 0.05
Delayed speech	+	+	-	< 0.02
Mental retardation	-	-	+	< 0.05
Hypotonia/Flaccidity	-	-	+	< 0.05
Spasticity				

For comparing quantitative data, Kruskal Wallis test and Mann Whitney tests were performed. A probability value (p=0.005) was considered statistically significant.

4- DISCUSSION

Corpus callosum is a unique fiber bundle in human brain. It is comprised of approximately 190 million axons that connect the left and right cerebral hemispheres. It is formed between the 7th and the 20th week of gestation. They cross the midline by the 12th week. Growth of anterior sections is evident in the 14th –15th week. Posterior sections begin to develop by the 18th –19th week (3, 7-9). By birth, cross-sectional area of the splenium and genu is uniform. The anterior and posterior callosal sectors are among the most rapidly developing white matter structures. If this process is disrupted, partial or complete

callosal agenesis may ensue. Large parts of the supra- and infra-tentorial brain are created during this critical period (3, 8). Agenesis of corpus callosum (AgCC) is one of the most common congenital brain malformations. Its frequency is about 1 in 4,000 individuals, and represents 3–5% of individuals assessed for neurodevelopmental disorders. It is characterized by the partial or complete absence of callosal fibers, and is accompanied by other white matter tracts malformations and multiple brain anomalies (8-12). Complete and partial AgCC can result from genetic, infectious, vascular, or toxic causes.

It accompanies chromosomal anomalies in 10% of patients, and 20–35% have recognizable genetic syndromes. The number of brain network connections determines the neurological and cognitive abilities of individuals. Reduction or loss of these connections leads to dramatic defect in behavior and functional development (7, 13, 14). In our study, we aimed to assess the role of fiber tractography and diffusion tensor imaging in evaluation of corpus callosum anomalies and correlate the callosal segmental fiber defects with clinical presentations of these patients.

In our study, we found that the most frequent clinical presentation is behavioral and social problems including ADHD and autism, which present in 32% and 23% of patients, respectively. Followed by seizures and developmental delay that were present in 21% and 18%, respectively. This is concordant with Schell-Apacik et al., Wahl et al., and Bénézit et al., who stated that variation in Probst bundles in partial agenesis, callosal fragments correlate with behavioral and cognitive disorders (2, 5, 10). Contrary to Schilmoeller et al., who found that mental retardation was the most common presentation in his study presenting 60% of patient complaints, which could be explained by the fact that most of his patients have correlate to to genetic and chromosomal association and only 33% of his patients have MRI evaluation,not all of them (14). We classified our patients according to the refined classification by Hanna et al., to provide accurate morphological classification (6). The heterogeneity of callosal morphologies is more accurately described by the inclusion of subclasses of corpus callosum abnormalities and is almost sufficient to characterize our entire cohort. We found that the most common class in our study is hypoplastic corpus callosum without dysplasia that coupled with the results of Neal et al., in their study where they found that 30.5% of their patients showed hypoplasia without dysplasia (4).

We also found that, 21.7% of our patients inherited and genetic backgrounds, which is concordant with many previous studies such as Schilmoeller et al., who stated that genetic and chromosomal association present as underlying etiology for Ag CC and dysgenesis of corpus callosum (DCC) (14). Regarding our results, associations of corpus callosum anomalies with other brain anomalies such as holoprosencephaly, hippocampal anomalies, septal and hindbrain malformations are common. This could be explained as corpus callosum development intra-uterine is formed between the 7^{th} and 20^{th} gestational week. Large parts of supra and infra-tentorial brain are formed during this period. This makes association with other brain anomalies possible which agrees with the findings of Schell-Apacik et al., Rummeny et al., and Alexander et al.'s studies (2, 3, 15). In this study, we found that partial AgCC and DCC usually involves the posterior segment of the fibers, which is concordant to Rummeny et al., who explain that callosal fibers follow "front-to-back rule" in development and interruption of the process of development will lead to incomplete formation of the

dorsal fibers (3). Using DTI and FT, we focused on bundles affected including the cingulum, mesial region, Probst bundles and sigmoid bundle. They were selected using a conventional region-based approach. We found that in patients with corpus callosum dysgenesis most of the major white matter bundles are relatively normal and showed preserved microstructure using fractional anisotropy and mean diffusivity that agreed with Bénézit et al., and Lee et al., who stated that in spite of abnormal arrangement of callosal fibers almost all of the white matter tracts are seen within normal with normal motor fibers and major interconnecting fibers in the brainstem (5, 16). We found that Probst bundles and Colpocephaly are associated with AgCC more than with DCC. They represent in (47%, 20%) in AgCC, and (3%, 11%) in DCC, respectively. Probst bundles are the longitudinal axonal fiber tracts of the corpus callosum that failed to cross the midline into the contralateral hemisphere and form ectopic fiber bundles along the dorsomedial aspect of lateral ventricle. Colpocephaly usually develops due to decreased white matter in the occipital cortex leading to secondary expansion of the posterior horns of the lateral ventricles.

Preservation of myelinated callosal tracts in hypoplasia or dysplasia maintains the structural integrity and prevents posterior expansion of lateral ventricles. This agreed with Neal et al., and Wahl et al., who stated that considerable variation has been found in the connectivity of Probst bundles and, in partial agenesis callosal fragments. These variations might correlate with behavioral and cognitive performance which would be very useful clinically, leading to early prognosis of developmental outcome and represent a potentially useful marker for severity of condition (4, 10). In our study most of the patients have behavioral and cognitive performance defect, the most common was autism and ADHD. Autism spectrum disorder (ASD) is a neuropsychiatric disorder with deficits in communication and social interaction in addition to stereotyped, restricted and repetitive behaviors. Both ACC and autism are developmental disorders with polygenic, heritable component. Autism may arise from an atypical connectivity and synapse formation in the brain, leading to its conceptualization as a category of disconnection disease. This creates a close link between autism and corpus callosum agenesis and dysgenesis.

This is concordant with our results that prove the connection between callosal anomalies and autism (17-21). Also, attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a prevalence of 5% in children and adolescents. ADHD is characterized by inattention, hyperactivity and impulsivity in addition to significant comorbid functional and psychosocial impairments. Neuroimaging of attention-deficit/hyperactivity disorder (ADHD) has revealed deviations of the corpus callosum in children and adolescents. Polanczyk et al., Cuffe et al., and Luders et al., stated that in their study, which agreed with our results (22-24).

As the main role of corpus callosum is the integration of various interhemispheric brain functions, including basic sensorimotor and high-level cognitive integration, we tried to use detailed meticulous DTI and FT evaluation of the callosal fibers. We focused on detection of the exact segment of fibers affected in corpus callosum, either fronto-rostral, caudal or whole body bundle affection and correlate the segmental affection with clinical presentation. We found that reduction of the fronto-rostral fibers is associated with social, behavioral and emotional deficits which clinically present in patients with attention defect and hyperactivity disorders (ADHD) or

patients with autism with significant p-value 0.001. This could be explained by the anatomical fiber distribution of this region that includes the connecting fibers of dorsolateral prefrontal cortex, middle frontal cortex and orbitofrontal cortex regarding the Brodmann atlas of the brain. This agreed with Wahl et al, Lee et al., and Nakata et al., who stated that anterior cingulate cortex aberrant connections might contribute significantly to the behavioral changes (10, 16, 25).

We found significant relation between clinical presentation with epilepsy and developmental motor defect and complete fiber loss in AgCC as well as caudal fiber defect in patient with DCC. This could be explained by the fact that anatomical location of interconnecting fibers of primary motor cortex and supplementary motor area, mostly pass through the isthmus and posterior mid body of corpus callosum according to Brodmann atlas. These findings were in agreement with Schell-Apacik et al., and Kim et al., in their studies where they also recorded the association of motor developmental delay and seizures in patients with caudal segment defect (2, 26).

Some limitations still exist in this study that lacks complete genetic and chromosomal work up. Also, there is a limitation in evaluation of whole brain volumetric changes which was not in the scope of this work and we will consider it in another work related to the same subject which may explain the difference of clinical presentation in spite of having the same radiological changes and the same white matter tract defect.

5- CONCLUSION

According to the results of our study, we can say that symptoms and manifestations associated with agenesis and dysgenesis of corpus callosum cannot be explained by the morphological changes only seen in conventional MRI. As a wide spectrum of neuropsychological deficits, including autism, ADHD and other diseases may result from affection of the integrity of callosal fibers. Fiber tractography and diffusion tensor imaging can be helpful in evaluation of the affected tracts changing the prognosis and line of treatment in this patient cohort.

6- CONFLICT OF INTEREST: None.

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