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MRI Evaluation of the Brain in Children with Attention Deficit and Hyperactivity Disorder; How to Hear the Whispers Early?

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Abstract

Background
Attention deficit and hyperactivity disorder (ADHD) is a disorder of the brain characterized by periods of inattention, hyperactivity and impulsive behavior. We aimed to evaluate the role of MRI of the brain in children with ADHD.

Materials and Methods
This prospective study included 100 children with clinical diagnosis of attention deficit and hyperactivity disorder according to the criteria of IDC-10. There were 79 males and 21females. Their ages ranged between 3 and 14 years old. A cohort of patients were referred from pediatric neurology unit to radiology department in El Minia University hospital, El Minia, Egypt, in the period between January 2017 and December 2017. All of them underwent MRI evaluation of the brain after approval of the ethical committee of our institution and completion of informed consent.

Results
MRI examination was positive in 66/100 patients and negative in 34 /100 patients. Corpus callosum dysgenesis was the most common finding in 19/66 patients, followed by temporal lobe pathology in 14/66 patients. Fronto-parietal or cerebellar atrophy was found in 11/66 patients. Tuber cinereum lesions, hippocampus sclerosis, heterotopia, pachygyria, hemimegalencephaly, Joubert syndrome and pineal cyst were a spectrum of findings among the remaining positive patients.

Conclusion
MRI of the brain in children with attention deficit and hyperactivity disorder will be the pivot for diagnosis. Not all patients had cerebellar or fronto-parietal atrophy as presumed before. Temporal lobe, corpus callosum and tuber cinereum must be looked for carefully.

Key Words: Attention deficit and hyperactivity disorder, Brain, Children, MRI.

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1- INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a clinically diagnosed condition. It is characterized by chronic excessive hyperactivity, impulsivity and inattention. It affect 5-7% of children and adolescents population. For a long time, it was classified as hyperkinetic disorder (HKD). There are three subtypes of ADHD which are predominantly inattentive, predominantly hyperactive/ impulsive and combined type (1). Clinical diagnosis of ADHD requires the presence of at least 6 symptoms of hyperactivity /impulsivity and at least 6 symptoms of inattention which are necessary for making the clinical decision of whether or not to treat. The high degree of heterogeneity in ADHD brings attention to the presence of many underlying causes for the condition. Neuro-radiological investigations began as a starting point for diagnosis of ADHD using structural and functional MRI (1- 3).

Neuroimaging techniques are increasingly being applied to the study of attention-deficit/hyperactivity disorder. Imaging of the brain anatomy of ADHD has become the main stay for diagnosis. For a decade, most studies have focused only on frontal-striatal regions and detection of smaller volume of the brain in the affected patients. As most published studies showed, there is a 3% to 4% global reduction in brain volume with abnormally small caudate nuclei (1). Our study aimed to answer two important questions: 1- Are there any brain anatomic abnormalities associated with ADHD? 2- Are there any developmental disorders that could be associated with the disease?

2- MATERIALS AND METHODS

2-1. Study design and population

Our study is a prospective study including 100 consecutive patients with clinical symptoms and signs supporting the clinical diagnosis of ADHD. There were 79 males and 21 females. Their ages ranged between 3 and 14 years old. They all referred from pediatric neurology unit to MRI unit at the radiology department in El Minia University hospital, Egypt, from January 2017 to December 2017.

2-2. Ethical consideration

A 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

All included children have six or more symptoms suggesting attention-deficit/hyperactivity disorder according to Wolraich et al., persisted for 6 months to a degree that is inconsistent with the developmental level and negatively impacts the social and academic activities of the child (3).

2-4. Methods

2-4-1. Patient preparation

Before MRI examination, all patients' parents were routinely questioned about any conditions that contraindicate MRI examination such as metallic prosthesis, clips or implants. They changed into cotton gown for examination. Patients' parents were asked about any condition that would interfere with anesthesia in patients that need anesthesia. An experienced anesthesia consultant (A.H.) supervised all of the anesthetic procedure 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 hours before the procedure.

2-4-2. MRI technique

MRI examination was performed for all patients using a 1.5 T Gyroscan Achieva (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 upon which the remaining pulse sequences were planned (localizing scan) was used. 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). Axial and 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). Sagittal and coronal T1WI with thin sections (2-3mm) with small field of view was done for patients with hypothalamic lesions, repeated after contrast administration of a standard dose (0.2 mmol/kg) of gadopentetate dimeglumine. Coronal 3D VIBE was used for confirmation of hippocampal sclerosis in some patients (TR 63/TE 7000; flip angle, 15°; field of view, 400 mm; slice thickness, 3 mm; section gap, 0.6 mm; number of slices, 32-40; image matrix 346 x 512 ; bandwidth, 490 Hz/pixel; 1 signal acquisition; scanning time, 24-28 seconds).

2-5. Data Analyses

Two experienced neuro-radiologists (N. F.), and (M.I.) with more than 10 years' experience in analysis and interpretation of MRI brain images interpreted all MRI data. All data were statistically described in terms of frequencies and percentage when appropriate. Correlation between MRI findings and clinical data was calculated using Chi-square test for qualitative data with the significant correlation set at p-value $\leq .05$. All statistical calculations were done using computer programs IPM SPSS software version 20.0.

3-RESULTS

Our study included 100 consecutive patients. There were 79 % males and 21% females. Their ages ranged between 3 and 14 years old. Their baseline characteristics and relevant history were tabulated in (**Table.1**). They were presented clinically by stigmata suggesting ADHD. Poor social relationships, hyperactivity and poor behavioral inhibition were the most common clinical presentation among our patient cohort (**Table.2**). MRI examination showed positive diagnostic data in (66%) of the patients and negative results in 34% of the patients.

Table-1: Baseline characteristics of patient cohort, (n=100)

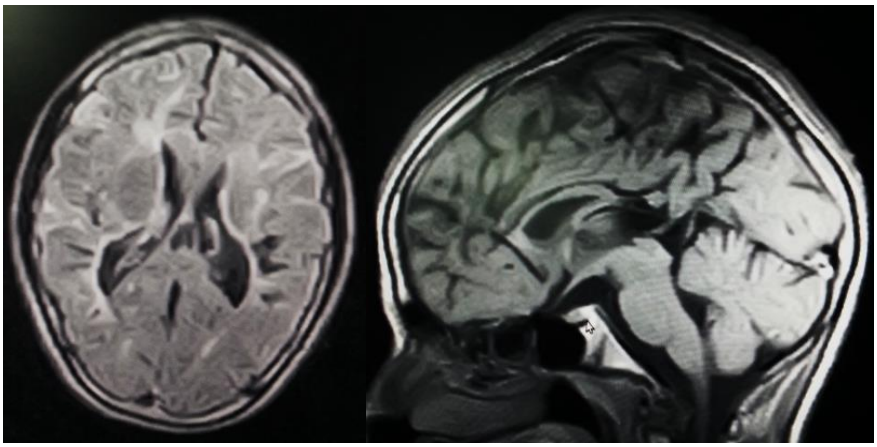
Data	Percent, total=100
Gender: Male Female	 79 21
Locality area Urban Rural	 63 37
Relevant history Obstructed labor Febrile convulsion Congenital infection	 36 24 16
Family history Positive Negative Not sure	 12 83 5

Table-2: Clinical presentation of ADHD patients (n=100)

Clinical presentation*	Number
Poor social relationships.	(82)
Hyperactivity	(74)
Poor behavioral inhibition.	(54)
Aggressive behavior.	(48)
Conductive disorders.	(46)
Lack of self-regulation.	(46)
Cognitive disorder.	(45)
Antisocial personality disorder.	(44)
Impaired response control	(37)
Learning disorders	(24)
Compulsive behaviors	(24)
Poor academic performance.	(23)
Anxiety and depression symptoms.	(23)
Separation fears.	(22)
Perfectionism.	(12)

*More than one symptom in one patient.

Corpus callosum dysgenesis was the most common finding in 19/66 patients presenting 28.7 %. Ten patients had reduction of girth of all segments of corpus callosum including body, genu and splenium (hypoplasia- corpus callosum) (**Figure.1).** Seven patients showed reduction of the girth of the rostral segment of the body with normal genu and splenium (dysgenesis of corpus callosum). Two patients showed hypoplasia of posterior segment and splenium.

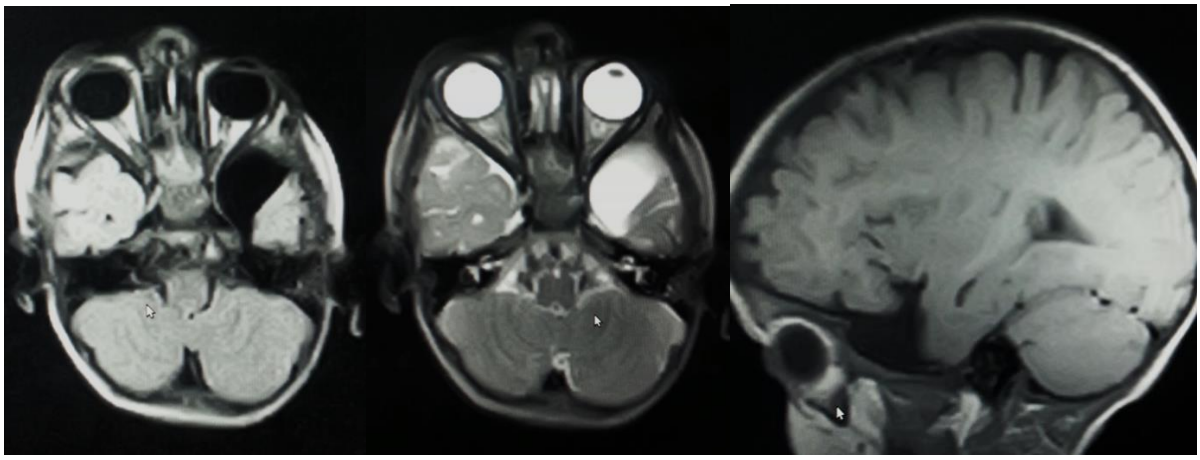


(a) (b)

Fig.1: A 4- year- old boy with hyperactivity and inappropriate response. a) Axial FLAIR shows reduction of the volume of white matter that showed abnormal bright signal, more pronounced at the frontal and occipital regions. b) Sagittal T1WI showed hypoplastic corpus callosum with marked reduction of the thickness of the fronto-rostral segments (Final diagnosis hypoplastic corpus callosum).

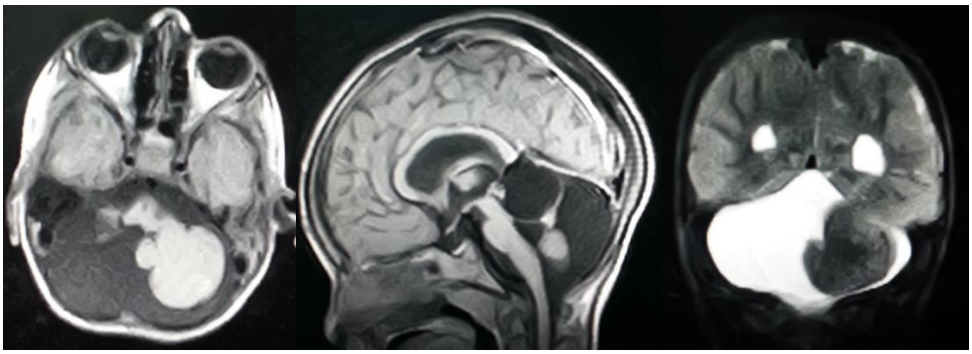
Temporal lobe pathology was the second common pathology encountered among our patients (14/66 patients). They include unilateral atrophic temporal lobe in four patients and bilateral atrophic temporal lobe in three patients. Arachnoid cyst **(Figure.2)** was seen in 5 patients, two of them had associated temporal lobe atrophy. Two patients had temporal lobe space occupying lesions. One of them proved to have astrocytoma and the other one could not be traced and final diagnosis

not known. Atrophic brain was encountered in 11/66 patients. Isolated frontoparietal atrophic change was the most common as it was seen in seven patients. Cerebellar atrophy was seen in 4 patients. Two had isolated cerebellar atrophy **(Figure.3)**, and the other two had associated findings. One had associated with rhombencephalic **(Figure.4)**, and the other one had associated Dandy Walker variant.



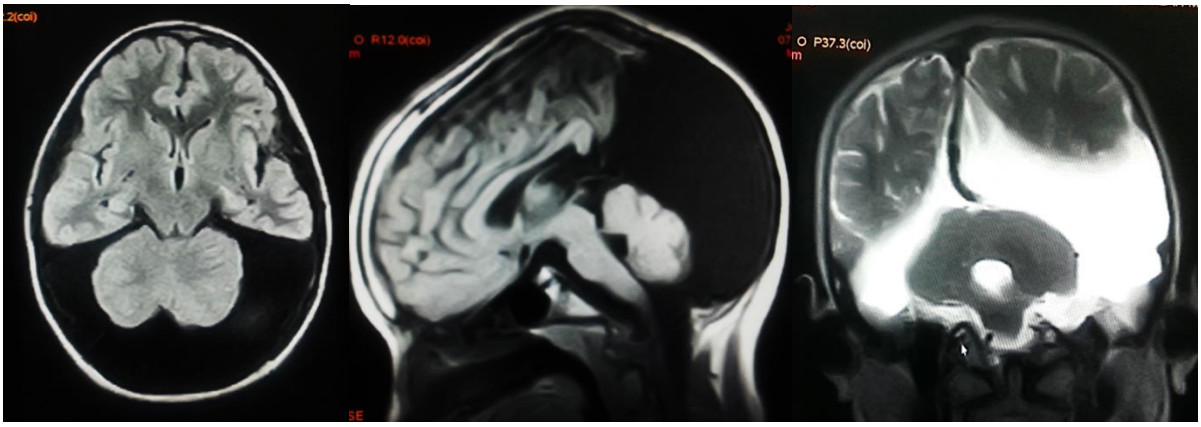
(a) (b) (c)

Fig.2: A 6- year- old male presented with hyperactivity and abnormal movement. a) Axial FLAIR showed widened left temporal arachnoid space with relative reduction in the size of left temporal lobe. b) Axial T2 showed high SCF of the cyst. c) Sagittal T1 showed the relative reduction of the left temporal lobe size (Final diagnosis left temporal lobe arachnoid cyst).



(a) (b) (c)

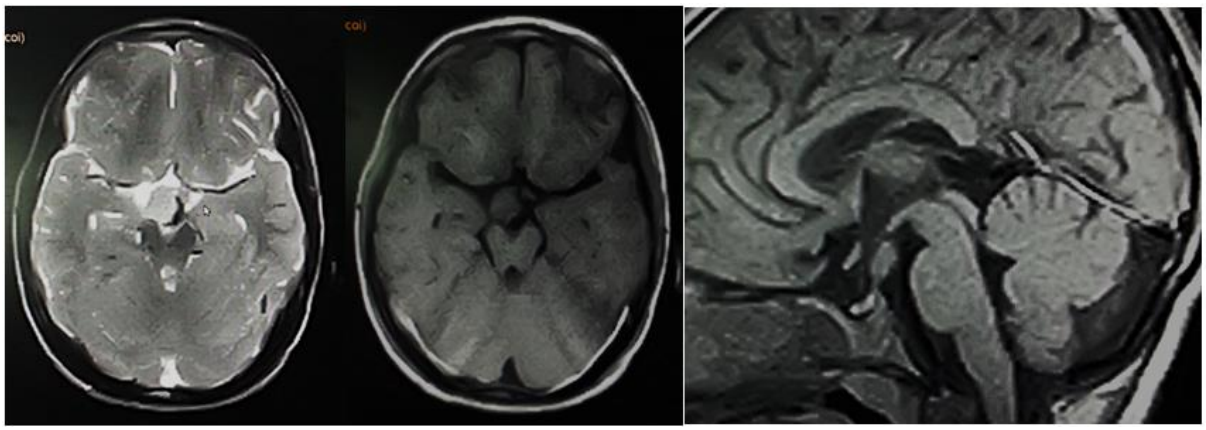
Fig.3: A 4- year- old male presented with hyperactivity, impaired response control, abnormal movement. a) Axial FLAIR showed markedly hypoplastic right cerebellar hemisphere with hypoplastic vermis. b) Sagittal T1WI showed markedly hypoplastic cerebellum, note the normal size and segmentation of corpus callosum, normal pituitary and normal tuber cinereum. c) Coronal T2WI showed the hypoplastic right cerebellar hemisphere and hypoplastic vermis (Final diagnosis right cerebellar hypoplasia).



(a) (b) (c)

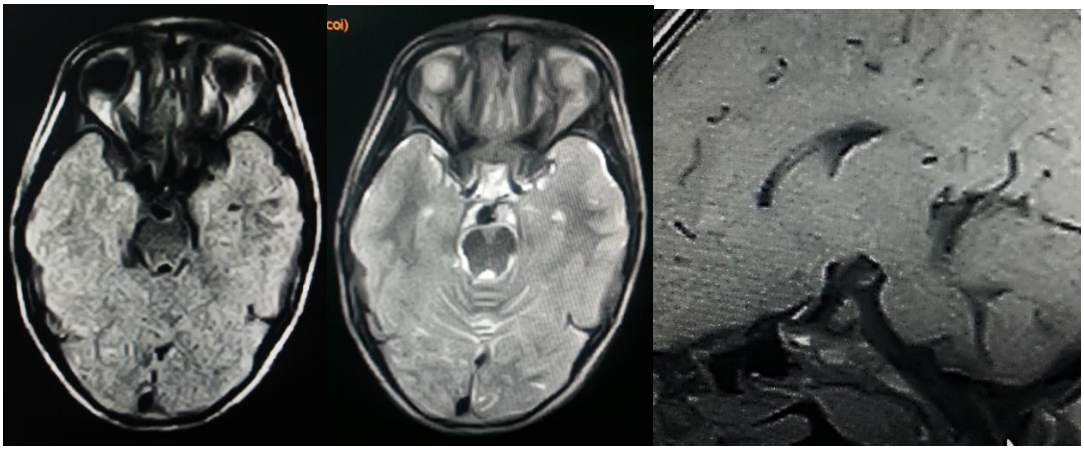
Fig.4: A 7- year- old male presented with impaired response control, ataxia and gait disturbance. a) Axial FLAIR showed markedly hypoplastic cerebellar hemispheres that are seen fused at the mid line. b) Sagittal T1WI showed the hypoplastic cerebellum associated with large cystic simulating lesion. c) Coronal T2WI showed the hypoplastic cerebellum fused at mid line (Final diagnosis cerebellar hypoplasia with rhombencephalic).

Tuber cinereum lesions were depicted in seven patients, five of them were finally diagnosed as hamartoma of tuber cinereum **(Figure.5)**, diagnosis was confirmed by MRS (not done in our facility), and assigned for follow-up. Cavernoma of tuber cinerium **(Figure.6)** was seen in two patients. They were diagnosed after detection of signal void of calcifications and marginal low signal of hemosiderin within the lesions. Hippocampus sclerosis was diagnosed in 5 patients. It needs the use of three-dimensional (3D) Volumetric Interpolated Breath-hold Examination (VIBE) sequence for more confident diagnosis, and measurement of the volume of hippocampus to confirm the diagnosis. An electroencephalogram (EEG) was done for these patients for further evaluation and they were positive. 3D VIBE showed high accuracy in diagnosis and short time utilization. Two patients showed bilateral hippocampal sclerosis and three showed unilateral hippocampal sclerosis.



(a) (b) (c)

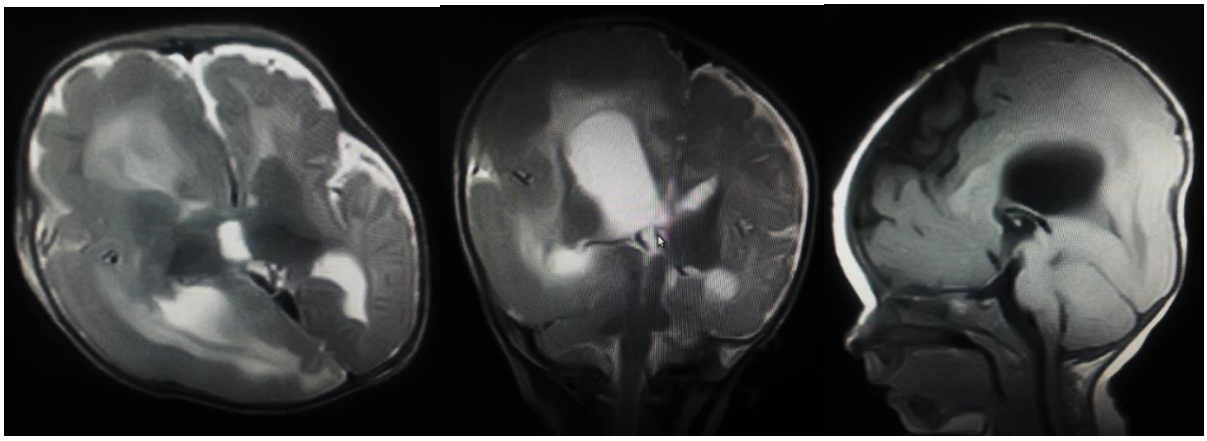
Fig.5: A 5- year- old boy with aggressive antisocial behavior and hyperactivity. a) Axial FLAIR and b) Axial T1WI show an isointense signal lesion at the right side of mid line filling the right side of the supra-seller cistern. c) Sagittal T1WI showed markedly thickened tuber cinereum. Note the normal girth and segmentation of corpus callosum (Final diagnosis hamartoma of tuber cinerium).



(a) (b) (c)

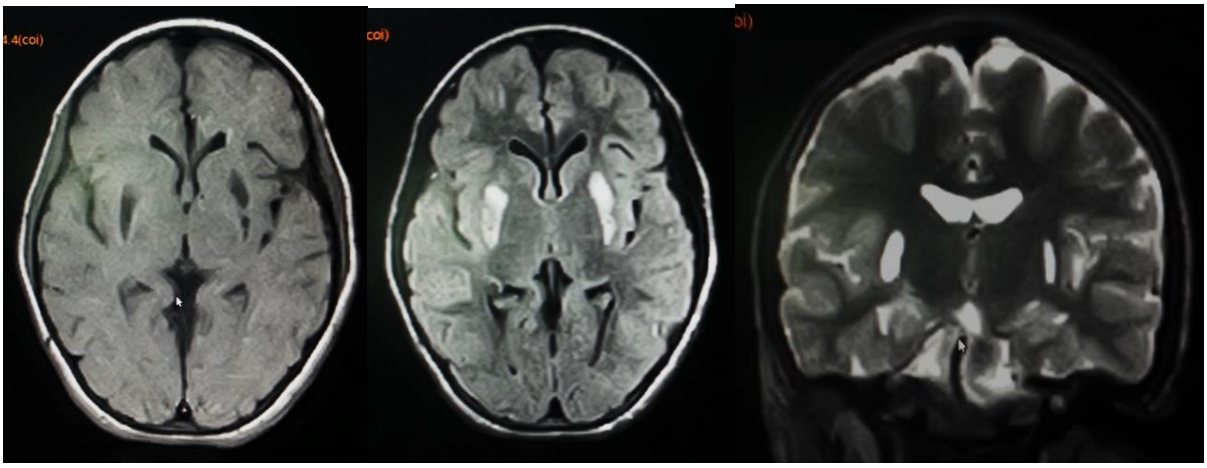
Fig.6: A 6- year- old boy with hyperactivity, impulsive action and inappropriate response. a) Axial FLAIR and b) axial T2WI show a well-defined low signal lesion at the right side of interpeduncular cistern. c) Sagittal T1WI showed markedly thickened tuber cinerium with marginal signal void of calcification (Final diagnosis cavernous hemangioma of tuber cinerium).

Heterotopia, Pachygyria, Leigh syndrome, and hemimegalencephaly (HME) were seen in two patients for each. Regarding heterotopia, one patient had focal cortical dysplasia and one patient had sub-ependymal band heterotopia. As regards HME patients **(Figure.7)**, one had isolated hemimegalencephaly, and the other one had associated corpus callosum dysgenesis. Patients with Leigh syndrome **(Figure.8)** showed abnormal high signal in basal ganglia and confirmed using laboratory investigations that showed high lactate levels.



(a) (b) (c)

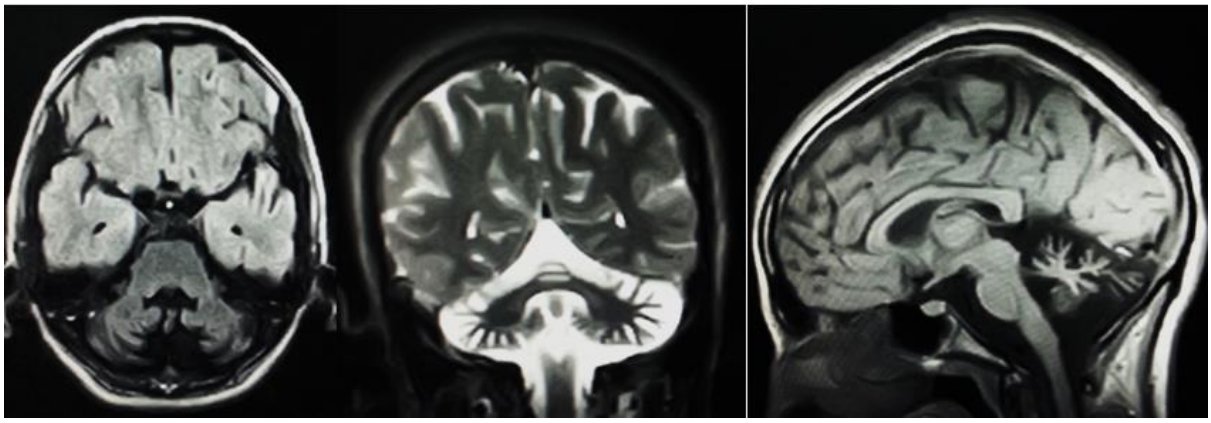
Fig.7: A 3- year- old male presented with hyperactivity and impaired response. a) Axial and b) coronal T2 relatively large sized cerebral hemisphere with smooth gyral appearance that is seen more notable at the parieto-occipital regions. c) Sagittal T1WI support the same findings, note the hypoplastic corpus callosum (Final diagnosis Hemimegalencephaly with Lissencephaly).



(a) (b) (c)

Fig.8: A 7- year- old female child presented with abnormal gait, poor academic performance and anxiety and depression symptoms. a) Axial T1 showed bilateral nearly symmetrical abnormal low signal involving both putamen. b and c) Axial and coronal T2WI showed bilateral high signal in the same area of lentiform nucleus at the putamen (Final diagnosis Leigh disease).

Concerning Joubert syndrome **(Figure.9)**, it was an unusual case with near normal mentality, and complaining of ataxia, and antisocial behavior with marked academic delay. Pineal cyst was seen in one patient, it was 1 cm in diameter and assigned for follow-up. All MRI findings were tabulated in (**Table.3**). Clinico-radiological correlation between the clinical presentation of patients and the radiological findings were detected in MRI of the brain.



(a) (b) (c)

Fig.9: A 14- year old female presented with impaired response control, learning disorders and ataxia. a) Axial FLAIR showed atrophic cerebellum and markedly hypoplastic middle cerebellar peduncles, vermis and molar tooth appearance of mid brain. b) Coronal T2WI showed the atrophic cerebellum and atrophic middle cerebellar peduncle. c) Sagittal T1WI showed markedly hypoplastic cerebellum, note the normal size and segmentation of corpus callosum and normal pituitary (Final diagnosis Joubert syndrome).

Table-3: Final MRI diagnosis of 100 patients with ADHD child

Findings	Number
Corpus callosum dysgenesis	19
Temporal lobe pathology: Atrophy Arachnoid cyst Space occupying lesion	14 7 5 2
Brain atrophy: Fronto-parietal atrophy Cerebellar atrophy	11 7 4
Tuber cinerium lesion: Hamartoma Cavernous hemangioma	7 5 2
Hippocampus sclerosis	5
Pachygyria Heterotopia Hemimegalencephaly Leigh syndrome Joubert syndrome Pineal body cyst	2 2 2 2 1 1
Unremarkable MRI	34
Total	100

4- DISCUSSION

In the last decade, Attention-deficit/hyperactivity disorder (ADHD) became the most common neuropsychiatric disorder among children. It occurs in approximately 3-9% of the childhood population. ADHD has been conceptualized as a neurological disorder of the prefrontal cortex and its connections. In fact, the dorsal frontostriatal circuits have been linked to cognitive control, whereas fronto-cerebellar circuits have been linked to timing. Neurobiological dysfunction of these circuits could lead to symptoms of ADHD (4, 5). However, like all psychiatric disorders are based on symptoms. They have a wide range of causes and susceptibilities. So neurobiological investigations are a necessary point for diagnosis. They have been the basis for an increasing number of structural as well as functional neuroimaging studies (1). The aim of our study was to answer a simple question: what are the anatomic substrates associated with combined type of ADHD? Our study was conducted on 100 children, 79 males, and 21 females. In spite of the limited number of patients we had higher incidence of disease among male patients than females which agrees with Edmond et al., who stated that boys are likely to be involved with ADHD around three times more than girls, which is almost approximately the same incidence in our study (5). We found that family history was positive in 17% of our patient cohort which is a considerable incidence percentage making heredofamilial element must be searched for, which is concordant with Mulder et al., and others who found that familiar vulnerability presents in families that had history of ADHD patients (6- 9). In our study, clinical presentations of ADHD had a wide spectrum including: poor social relationships, hyperactivity and poor behavioral inhibition. Impaired response control, poor academic performance and learning disorders are also recorded. We tried to depict the structural and anatomic brain changes and correlate them with the presenting clinical manifestations. Our results showed that patients with corpus callosum dysgenesis have poor self-regulation and impulsive

behavior. This could be explained by the neurobiological function of corpus callosum. Corpus callosum fiber tracts are connecting between the two cerebral hemispheres. It allows for transfer and integration of sensory, motor and cognitive information. Disruption of these connections usually leads to impulsivity and cognitive disorder which is consistent with Neal et al., and others who stated that corpus callosum dysgenesis usually correlated with impaired response control (10 -12). Corpus callosum dysgenesis group of patients have near normal mentality. They present the most common pathological finding (28.7%) of our patient cohort. This could be explained by the fact that agenesis and dysgenesis of corpus callosum is one of the most frequent brain malformations. It is a heterogeneous condition that may be seen as an isolated entity or as one manifestation of congenital syndrome which is in agreement with Doherty et al., and Mohapatra et al., who stated that some patients with agenesis or dysgenesis of corpus callosum may show no developmental delay, and normal intelligence with mild behavioral or social problems as well as the attention-deficit-hyperactivity disorder (ADHD) (10, 13,14). As regards hypothalamic region affection, our results showed that thought and attention problems are correlated with the presence of hypothalamic lesion regardless of the underlying pathological type. This agrees with Castellanos who stated that cortico-striato-thalamo-cortical (CSTC) circuits are responsible for selection, initiation, and execution of complex motor and cognitive responses. Also, this is consistent with the results of Fortier et al., and Van der Meer et al. who stated that the biological changes through hypothalamic-pituitary-adrenal (HPA) axis in case of increased circulating cortisol level may result in several psychiatric disorders and significant behavioral changes (1, 15, 16). Our results showed that poor memory, poor academic performance and learning disorders are usually associated with temporal lobe pathology or reductions in volume of frontal or temporal cortex. This is in agreement with Castellanos, Cortese et al., and Angriman et al.'s reports which confirmed that most ADHD patients have reduction in the pre-frontal and occipital cortex volume (1, 4, 17). In our study, we have seen heterotopia, pachygyria and hemimegalencephaly in two patients for each. MRI can easily diagnose migration, proliferation and sulcation defects and differentiate between them and the simulate picture of vasculitis. In patients with focal cortical dysplasia sub-ependymal heterotopia appeared as abnormal signal of gray matter within the periventricular white matter and within the parietal subcortical white matter.

The proliferation defect in hemimegalencephaly and pachygyria can be diagnosed by the discrepancy between the size of both cerebral hemispheres in hemimegalencephaly patients and alteration of the shape and thickness of the gyri in pachygyria patients. This is in agreement with Abdel Razek et al., who stated that interruption of normal developmental sequences either due to defective proliferation, migration, or organization of the cortex can be easily diagnosed by neuroimaging and MRI which was proved to be a valuable tool in their diagnosis, and differentiation between them and vasculitis which may have simulating picture for focal cortical dysplasia picture. This is also in agreement with Duerden et al. who found that there is significant increase in cortical thickness in patients with ADHD (18-20). As regarding Joubert syndrome, there was an interesting case where the patient presented with anti-social behavior suggesting ADHD associated with ataxia. Using MRI imaging of the brain we detected the atrophic cerebellum, and markedly hypoplastic middle cerebellar peduncles. The

characteristic molar tooth appearance of mid brain also noted that is concordant with what was stated by Abdel Razek and Castillo in their article about hind brain malformations where they classified Joubert syndrome as a combined cerebellar and brain stem malformation (21). Finally, we can say the small number of the sample that was one of the limitations of this study did not allow us to make a full judgement on all brain changes associated with ADHD. Since the study was limited to children's population which needs anesthesia and full consent from parents to do the MRI examination. We also considered that not using functional MRI including Diffusion-weighted imaging (DWI), Magnetic resonance spectroscopy (MRS), and tractography is one of the most important limitations in this work. In fact, we will consider them soon in another coming work, as recent advances in MRI could be used in evaluation of different metabolic diseases, autism and ADHD simulating condition such as Gusher disease. Many authors such as Abdel Razek et al., and Lea et al. stated that there is significant difference in the apparent diffusion coef- ficient (ADC) value of normal brain, and brain of children with metabolic diseases like Gaucher disease. This may help in differentiation between them and ADHD patients who require a completely different treatment pathway (22-25). Also, the application of other functional MRI studies using BOLD technique in evaluation of brain function of children and adolescents with ADHD which may have altered regional brain function and be associated with executive dysfunction as stated by Li et al., may help our understanding of the relationships between neural substrate and executive function in ADHD (26).

5- CONCLUSION

According to the results, MRI evaluation of the brain in patients with attention-deficit/hyperactivity disorder proved to be very useful. Indeed, not all patients of ADHD had cerebellar or frontoparietal atrophy as presumed. Other regions of the brain must be searched carefully according to the specific clinical presentation. Functional MRI including DWI and MRS as well as tractography must be supervised in these patients to evaluate the white matter tracts in future studies.

6- CONFLICT OF INTEREST: None.

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