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EEG changes and neuroimaging abnormalities in relevance to severity of autism

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ABSTRACT

Background: Autism is currently viewed as a genetically determined neurodevelopmental disorder although its definite underlying etiology remains to be established.
Aim of the Study: Our purpose was to assess autism related morphological neuroimaging changes of the brain and EEG abnormalities in correlation to the degree of disease severity.
Patients and Methods: Seventeen cases with classic autism, 13 males and 4 females were included in the study. Severity of the disease was assessed both clinically and by Childhood Autism Rating Scale (CARS). MRI changes and EEG abnormalities were detected in seven patients, mostly severely and moderately affected.
Results: Hypoplasia of cerebellar vermian lobules is the most replicated MRI abnormality in our patients (18%). Periventricular white matter dysmyelination is detected in 12% of studied cases. 29% of the cases have EEG abnormalities. Head circumference above 97th centiles is detected in 18% of cases. The increased head circumference, when in combination with EEG abnormalities, positively correlates with the degree of disease severity.
Conclusion: Although, no definite correlation could be established between the studied parameters and disease severity, most patients in the present study who exhibited MRI abnormality, EEG changes and/or increased head circumference (H.C) manifested severe form of autism. The absence of correlation may be attributed to lack of statistical power, resulting from small sample size. However, the correlation was not solidly excluded therefore, the recommendation of further neuroradiological evaluation as well as the implementation of newer techniques, might help future elucidating the etiology of autism.

Key Words:

Autism, MRI, EEG, brain development.

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INTRODUCTION

Autism is a neuropsychiatric disorder of social, cognitive and language development. Autism Spectrum Disorders (ASDs) (OMIM 608638)[1] are diagnosed on the basis of qualitative abnormalities in social, communicative and imaginative behaviors and the presence of repetitive

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and stereotyped patterns of interests and activities. Diagnosis is complicated by the varied manifestation of these core deficits, by wide variation in ability level and by developmental changes[2]. Structural neuroimaging studies done by means of magnetic resonance imaging (MRI) have provided important insights into the neurobiological basis for autism[3]. MRI is the method of choice to investigate structural brain anatomy and development in autistic patients as it is a non-invasive technique that can investigate human brain morphology[4], although autistic disorders were eventually recognized as disorders of brain functioning, any adequate neurobiological model of autistic disorder has to account for the association with degree of severity, epilepsy, EEG changes and MRI abnormalities.[5]

Head circumference is increased in a proportion of individuals of autism. The MRI and head circumference changes are apparent from about 3-4 years of age. Age-related changes in brain volume in autism are complex and appear to be abnormal from infancy into adulthood. Diffuse differences in total and regional gray and white matter volumes are found.[6]

Hyperplasia was present in cerebral gray matter and cerebral and cerebellar white matter in early life in patients with autism[7]. Preliminary evidence for disproportion in the grey matter to white matter ratio and suggestion of regional variability in increased brain volume makes it unclear whether this abnormality is due to overproduction of cells which subsequently do not undergo selective cell death, or whether the primary problem is a failure of synaptic pruning.[8]

Estimates of the proportion of autistic individuals affected with EEG changes vary, but by adulthood about one-third of individuals with autistic disorders have developed epilepsy. Abnormal EEG findings can be found in as many as 43% of autistic patients, particularly in those with severe degree where seizures are estimated to occur in as many as 30% of children with autistic disorder. However, there is an observation that possibly 15-20% of children with autistic disorder without seizures have an epileptiform EEG has raised the possibility of subclinical seizures and also explain to some extent the acquired aphasia usually associated with EEG abnormality.[9]

The aim of the present study is to correlate severity of the disease to EEG changes, neuroimaging abnormalities and increased head circumference among our studied patients with autism.

PATIENTS AND METHODS

The study included seventeen cases diagnosed as autistic among patients frequenting the clinical genetics clinic, NRC. All patients met the diagnostic criteria of autism as defined in International Classification of Diseases, 10th edition (ICD-10).[10]

The studied cases comprised 13 males and 4 females, their ages ranged from 3 to 11 years. Full explanation of the study has been provided to their parents and written consents have been obtained.

For each case the following were conducted:

- Three generations pedigree construction and analysis including consanguinity, similar conditions and other affected members in the family.

- Complete history including parental occupation, conceptional and delivery histories, exposure to drug intake, fever and trauma.
- Detailed clinical examination.
- Anthropometric measurements including height, weight and head circumference.
- Rating the severity of autism using Childhood Autism Rating Scale (CARS)[11]. Accordingly patients were classified into three Groups; mild, moderate and severe.
- Magnetic resonance brain imaging (MRI) and or computed tomography (CT).
- Electroencephalogram (EEG).

RESULTS

Our study included 17 cases, 4 females and 13 males. Cases were subjected to pedigree analysis, proper clinical examination, anthropometric measurements, CARS, MRI &/or CT and EEG. Positive consanguinity was found in 23% of studied cases 18% showed macrocephaly. According to CARS evaluation 18% of cases were classified as mild, 29% as moderate and the rest were of severe forms (53%). EEG changes were exhibited by 35% of cases, all showed epileptogenic foci and two cases had cerebral dysrythemia. Forty one percent (41%) of cases showed neuroimaging abnormalities. These abnormalities include, vermal hypoplasia (Figures. 1-A,B), periventricular white matter dysmyelination (Figure. 1C), supratentorial hydrocephalus and central and cortical brain atrophy (Figure. 1D).

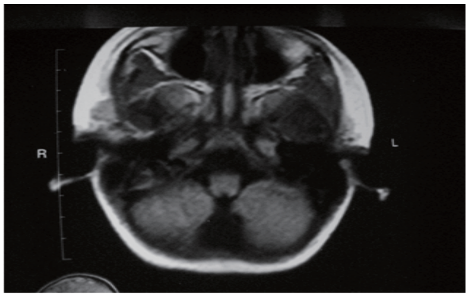

Fig. 1A: Axial T1 showing cerebellar vermal hypoplasia.

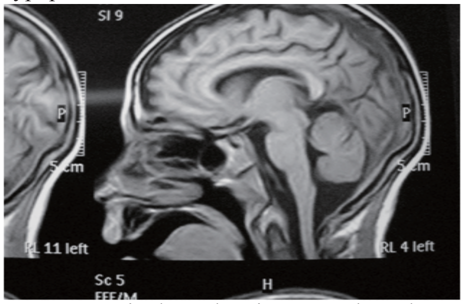

Fig. 1B: Sagittal T1 showing normal cerebrum, corpus callosum and brain stem, isolated vermal hypoplasia.

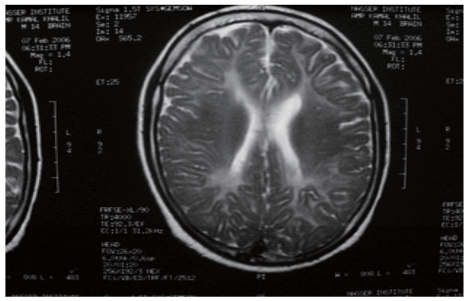
Fig. 1C: Axial T2 showing dysmyelination around frontal and occipital hornes of lateral ventricles.

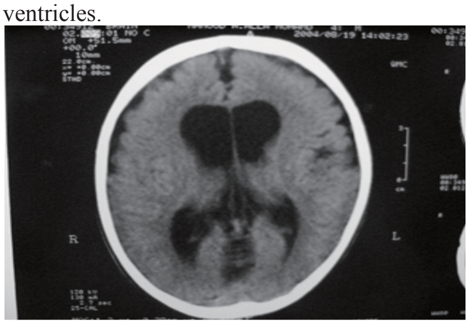

Fig. 1D: CT showing mild prominent sulci of fronto-parietal region and dilated ventricles especially frontal horns indicating central and cortical atrophic changes.

Only 18% of the cases share the EEG and MRI changes, but most of the cases that showed EEG changes and or MRI abnormalities suffered severe or moderate autism as evaluated by CARS. However, there was only one case that has mild autism as evaluated by CARS and showed MRI abnormalities.

Table 1: Shows the distribution of EEG, macrocephaly, neuroimaging findings and CARS evaluation among the studied patients.

Case No	Age (yrs)	Sex	Cons -ang.	Macro -Ceph.	CARS	EEG	Neuroimaging abnormalities
1	7	♂	-ve	+ve	Mild	Normal	Normal
2	11	♂	-ve	-ve	Severe	Right tempro- parietal epileptogenic activity without 2ry generalization	Periventricular white matter dysmyelination
3	10	♂	-ve	-ve	Moderate	Normal	Normal
4	4	♀	-ve	-ve	Moderate	Norma	Normal
5	9	♂	-ve	-ve	Mild	Normal	Normal
6	9	♀	-ve	-ve	Severe	Epileptogenic focus	Normal
7	6	♂	+ve	-ve	Severe	Generalized cerebral dysrrythmia, epileptogenic in nature	Normal
8	5	♂	+ve	-ve	Severe	Normal	Normal
9	4	♂	+ve	-ve	Mild	Normal	Periventricular white matter dysmyelination
10	6	♂	-ve	-ve	Moderate	Severe cerebral dysrrythmia, no epileptogenic focus	Normal
11	3	♂	-ve	+ve	Severe	Bilat. subcortical fronto-tempro-parietal epileptogenic discharge	Supratentorial hydrocephalus with no intra cranial space occupying lesion
12	6	♂	-ve	+ve	Moderate	Normal	Normal
13	3	♀	-ve	-ve	Severe	Normal	Central and cortical brain atrophy
14	6	♂	-ve	-ve	Severe	Normal	Normal
15	5	♂	+ve	-ve	Moderate	Normal	Vermal hypoplasia
16	6	♂	-ve	-ve	Severe	Epileptogenic focus	Vermal hypoplasia
17	11	♀	-ve	-ve	Severe	Normal	Vermal hypoplasia

DISCUSSION

Brain MRI may be helpful in the clinical assessment of global developmental delay as the Practice Committee of the Child Neurology Society Outlined in 2003[12]. Recent neuroimaging studies have shown that a contributing cause for autism may be abnormal brain development beginning in the infant's first months[8]. Studies have shown that many major brain structures are implicated in autism. This include; the cerebellum, cerebral cortex, limbic system, corpus callosum, basal ganglia and brain stem.[13]

However, cerebellar abnormality in autism has been shown consistently from autopsy and MRI[14]. Hypoplasia of cerebellar vermian lobules is the most replicated MRI abnormality among our studied patients 3/7. Saitoh and Courchesene[14] identified two subgroups of autistic patients, hypoplasia and hyperplasia of cerebellar vermian lobules.

Gaffney et al.[15] reported that cerebellae of autistic patients were smaller when compared to normal subjects.

Hashimoto et al.[16] studied the development of the brain stem and cerebellum in autistic patients, these structures were significantly smaller in autistic patients than in controls and they suggested that significant changes took place in the posterior fossa brain structures in the prenatal period in autistic children, but were not progressive.

A detailed morphometric analysis of cerebellum in autism with and without macrocephaly was done by Cleavingen et al.[17] a trend was noted in macrocephalic individuals with autism consistently exhibited slightly smaller cerebellar volume when compared to individuals with benign macrocephaly. However, Hrdlika[3] suggested that autistic individuals have large total brain, cerebellum and caudate nucleus volumes, but corpus callosum is reduced.

Effects of early midline cerebellar lesion on cognition and emotional functions in the rats were carried out by Bobee et al.[18] they concluded that the cerebellar vermis is involved in motor control, attentional capabilities and emotional behavior.

Their result strengthen the idea that the cerebellar vermis is involved in autism as already suggested by Caston et al.[19] as well as emphasizes the possible correlation of the cerebellar affection with disease severity.

Ritvo et al.[20] counted Purkinje cells in the cerebellum of four autistic cases and three male controls. Autistic cases showed a decreased number of Purkinje cells in the cerebellar hemisphere and vermis. Kemper and Bauman[21] also reported on alterations in the cerebellum, all autistic cases showed decreased numbers of purkinje cells. Fatemi et al.[22] were the first to examine the size of the cerebellar purkinje cells. Blocks of the cerebella of five adult male autistic subjects were compared with those of five age- and sex-matched controls. A 24% decrease in mean Purkinje cell size was found in the autistic Group.

All those studies of cerebellar intrauterine developmental affection in autistic cases points to its involvement in disease development. The above studies were mostly done on mentally retarded cases[23] which was one of the motives for our trials for correlation.

Other reports did not consistently show smaller midsagittal cerebellar hemispheres[24] or vermis[25-31] in autism. This lack of agreement in cerebellar segmentation among neuroimaging studies might be partially explained by using different MRI systems, as was reported by Lotspeich et al.[32]

It is important to keep in mind that generally these studies have not accounted for IQ as a confounding factor.[30]

Periventricular dysmyelination of white matter was exhibited by two patients in the current study 2/7. Such observation was replicated by Miyazaki and Hashimoto[33], who showed hyperintensity areas on T2 weighed images at the occipital lobe in 3 patients of autism. Because the hyperintensity areas are age dependent, they suggested that it may result from delayed myelination in the central nervous system. A developmental study of the structural integrity of white matter in autism was carried out by Keller et al.[34], who showed reduction in the structural integrity of white matter that persist into adulthood. They claimed that such reduction may underlie the behavioral pattern observed in autism. This again could be in favor of possible correlating of white matter integrity to disease severity.

Thirty five percent (35%) of our patients showed EEG changes, most of them were severe forms of the classic autism. Not all the affected patients exhibited seizures, however, they may manifest late into adulthood. Such finding is in agreement with Hardan et al.[35] who suggested that idiopathic autism is at high risk for epilepsy and by adulthood about one third of individuals with autism have developed epilepsy. Between 15 and 36% of children with autistic disorder (AD) but without epilepsy show EEG abnormalities, these are identified more frequently if EEGs are repeated or if magnetoencephalography is used as this is more sensitive than EEG.[36]

An increased prevalence of macrocephaly defined by occipito –frontal circumference (OFC) is a constant finding in autism, several possible mechanisms have been proposed, the most compelling being early brain overgrowth.[37]

Three cases among our patients had OFC > 97th percentiles, their ages were 3, 6 and 7 yrs at time of presentation and measurement, two of them have severe form of autism (according to CARS). Courchesene et al.[8] evaluated H.C of 48 patients with autistic disorder (AD) aged 2-5 y, compared to A Control Group, 59% of autistic patients showed accelerated H.C growth compared to 6% of normal individuals. A similar study done by Redcay and Courchesene[38] showed that the greatest deviation of H.C and brain size from normal is largely restricted to the first years of life (2-5y), study of older autistic H.C reflects the outcome rather than the process. Abnormally accelerated rate of H.C and brain size may serve as an early warning signal of risk of autism.[8]

Reviewing of literature and current study show that neuroimaging changes in autism are inconsistent and contradictory. Most patients of the present study who exhibited MRI abnormality, EEG changes and increased H.C were of severe form of autism, however such alteration was observed even in mild form.

The present study attempted to provide a certain correlation between the studied parameters and severity of the disease. Although some consistent results emerge, the majority of the data remains equivocal. This may be due to lack of statistical power, resulting from small sample size as well as the heterogeneity of the disorder itself and to the inability to control the potential confounding variables such as gender, mental retardation, epilepsy and medication status and importantly, to the lack of consistent design in histopathological quantitative studies of autism published to date.

In conclusion, the present study highlighted the importance of EEG, MRI and measurement of H.C as further investigation of different brain structures could contribute to the disparate findings. However, the underlying neurobiological basis remains elusive. The implementation of newer techniques such as design based stereology, large scale analysis of gene expression and evolving novel volumetric method to examine the size of the corpus callosum hold great promise and might eventually result in the elucidation of the etiology of autism.[39]

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