

# Brain MRI Findings in Children (2-4 years old) with Autism

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## Abstract

Autism is a neurodevelopmental disorder with a range of clinical presentations, from mild to severe, that is now classified in a broader class of disease called "autism spectrum disorders" (ASD). The aim of this study was to investigate Brain MRI findings in children (2-4 years old) with autism. The sample of the study included 40 autistic children aged 2 to 4 years whose disease was confirmed by a fellow psychiatrist based on the diagnostic criteria of autism spectrum disorders DSM IV-R. Having explained the study to parents and after obtaining their consent, a questionnaire was completed and a three-dimensional brain MRI was performed for each patient in the radiology department of Ghaem or Imam Reza hospitals. From among the 40 patients, 25 patients had a history of convulsion. Among the other patients, 4 patients (10%) suffered from simple febrile convulsion (simple FC), 2 cases from complex febrile convulsion (complex FC), 6 cases (15%) from TCG and 3 (7.5%) from Landau-Kleffner syndrome (LKS). Of the 15 patients with a history of convulsion disorders, 5 patients (12.5%) used phenobarbital, 4 patients (10%) took valproate and 2 patients (5%) were treated with multi-drug regimen. Although, we did not measure white matter connections, lesions in such neuroanatomic pathways may be causal factors of behavioral and

emotional dysfunctions in autistic patients. Finally, it is also important to understand how WMH severity changes over time.

**Key words:** MRI, Brain, Children, Autism

Please cite this article as: Mohammadi M. H. Et al. Brain MRI Findings in Children (2-4 years old) with Autism. *World Family Medicine*. 2017; 15(8):119-124. DOI: 10.5742/MEWFM.2017.93055

## Introduction

Autism is neurodevelopmental disorder with a range of clinical presentations, from mild to severe, that is now classified in a broader class of disease called "autism spectrum disorders" (ASD). The most common clinical ASD sign is impaired social interaction, which is associated with verbal and non-verbal communication deficits and stereotyped behaviors [2]. In most cases, it is not presently possible to detect a known or specific etiology; these are referred to as non-syndromic autism [1]. The clinical relevance of MR scanning in children with ASD is still an open question and must be considered in light of the evolution of this technology. In 2000, MRI was judged to be of insufficient value to be included in the standard clinical evaluation of autism according to the guidelines of the American Academy of Neurology and Child Neurology Society [1]. This consensus stated that the prevalence of lesions detected by MRI in children with autism has been reported to be similar to normal control subjects [2]. However, this statement was based on results obtained from small samples of patients and, more importantly, included mostly insufficient MRI sequences. An adequate brain MRI interpretation must include at least three different sequences (T1, T2, FLAIR) in three different planes. Yet, there are few clinical radiological studies with complete clinical MRI examinations in children with ASD. For example, in some small groups of children with ASD, some radiological MRI anomalies were described, such as accentuated Virchow–Robin space [3], acrocallocal syndrome [3], pachygyria [3] macrogyria and polymicrogyria [3]. However, until now, no reliable data has been available regarding the prevalence of MRI abnormalities in a large sample of patients with non-syndromic ASD.

In addition, in order to determine if the MRI abnormalities detected in the present population of children with non-syndromic AD could be also observed in a normal population of children. The aim of this study was to investigate Brain MRI findings in children (2–4 years old) with autism.

## Methods

The sample of the study included 40 autistic children aged 2 to 4 years whose disease was confirmed by a fellow psychiatrist based on the diagnostic criteria of autism spectrum disorders DSM IV-R. Having explained the study to the parents and obtained their consent, a questionnaire was completed and a three-dimensional brain MRI was performed for each patient in the radiology department of Ghaem or Imam Reza hospitals. Then brain MRIs were studied by fellow radiologist and the executor of the project. Brain MRIs of each patient were compared with the brain MRI of a child of the same age who did not have autism spectrum disorders and was under imaging for any other reason (trauma, infection, headache, etc.). The volume of frontal lobes and amygdala in each side were specified and then analyzed.

Quantitative analysis (Statistical Parametric Mapping = SPM) was employed for volumetry. In this method,

quantitative analysis was Voxel-based analysis, i.e. Voxels situated in the same spatial location were compared with each other, and the value of each voxel represented the probability of belonging to GM, WM or CSF. The method was implemented in a toolbox with the same name, SPM version 8.0. A very important step in quantitative analysis method of SPM was Normalization. On the basis of the existing atlases in SPM, MRI images of healthy and diseased individuals were normalized in such a way that all images of this stage were overlapped in terms of spatial coordinates. To do this step, SPM used Affine transformation matrix that was specific to each person under study (healthy and diseased) (44).

Software WFU\_PickAtlas version 3.0 and software Easy Volume were of the features available in the toolbox SPM. This software was applied for creating standard mask images based on Talairach and Tournoux Atlases and calculating the volume of gas. Among the areas in WFU\_PickAtlas, it could be referred to the areas considered in the study that included: Amygdala, Frontal Lobe and whole brain. The atlas was based on MRI images of a mature and healthy adult. In this study, the population under study was 2–4 years old children. That was why the Hammers Atlas was used here, because it was applied for 2–4 years old children and was available in NIHPD database (NIH Pediatric MRI Database). Using the Atlas, indexes of the intended areas were extracted and standard mask images were created using image processing toolbox in MATLAB. Changes in the shape and size (deformation) of the standard masks had to be so that it could be specifically used for volumetric of MRI images of patients under study. For this purpose, affine transformation matrix described earlier was employed for reverse conversion. In other words, this matrix that was specific for each person in the study was implemented on standard masks to create specific masks. When these steps were completed, the software Easy Volume was used to determine the volume of specific masks.

All children were evaluated by a pediatric neurologist, a clinical geneticist and a child psychiatrist. In addition, the recommended biological and medical screenings for ASD were performed, including high-resolution karyotyping, DNA analysis of FRA-X and normal standard metabolic testing (plasma and urine amino and organic acid analysis, urine glycosaminoglycans (GAG) quantitation, urine oligosaccharide, purine and pyrimidine analysis, and creative guanidoacetate urine analysis).

MRI was performed with a 1.5 Tesla (Sigma General Electric) scanner using the following sequences: 3D T1-weighted FSPGR sequence (TR/TE/TI/NEX: 10.5/2.2/600/1, flip angle 10u, matrix size 2566192, yielding 124 axial slices and a thickness of 1.2 mm, field of view 22 cm), axial and coronal FSE T2-weighted imaging (TR/TE: 6000/120, 4 mm slices, 0.5 mm gap, field of view 22 cm) and coronal FLAIR sequences (TR/TETI: 10000/150/2250, 4 mm slices, 1 mm gap, field of view 24 cm). MRI studies were performed during sleep induced by premedication (7 mg/kg of sodium pentobarbital) for all AD children to obtain immobility during scans. Signal intensities on T1, T2, and

proton density-weighted images relate to specific tissue characteristics. For example, the changing chemistry and physical structure of hematomas over time directly affects the signal intensity on MR images, providing information about the age of the haemorrhage. The most common pulse sequences are the T1-weighted and T2-weighted spin-echo sequences. The T1-weighted sequence uses a short TR and short TE (TR, 1000msec, TE, 30msec). The T2-weighted sequence uses a long TR and long TE (TR, 2000msec, TE, 80msec). The T2-weighted sequence can be employed as a dual echo sequence. The first or shorter echo (TE, 30msec) is proton density (PD) weighted or a mixture of T1 and T2. This image is very helpful for evaluating periventricular pathology, such as multiple sclerosis, because the hyperintense plaques are contrasted against the lower signal CSF. More recently, the FLAIR (Fluid Attenuated Inversion Recovery) sequence has replaced the PD image. FLAIR images are T2-weighted with the CSF signal suppressed. When reviewing an MR image, the easiest way to determine which pulse sequence was used, or the "weighting" of the image, is to look at

the cerebrospinal fluid (CSF). If the CSF is bright (high signal), then it must be a T2-weighted imaged. If the CSF is dark, it is a T1-weighted or FLAIR image. Pathologic lesions can be separated into 4 major groups (solid mass, cyst, blood, fat) by their specific signal characteristics on the three basic images: T2-weighted, FLAIR, and T1-weighted. Since studies have shown that T2-weighted images are most sensitive for detecting brain pathology, patients with suspected intracranial disease should be screened with T2-weighted spin-echo and FLAIR images. T1-weighted images are needed only if the preliminary scans suggest hemorrhage, lipoma, or dermoid. The axial plane is commonly used because of the familiarity with the anatomy from CT. Coronal views are good for parasagittal lesions near the vertex and lesions immediately above or below the lateral ventricles, temporal lobes, sella, and internal auditory canals. The coronal plane can be used as the primary plane of imaging in patients with temporal lobe seizures. Sagittal views are useful for midline lesions (sella, third ventricle, corpus callosum, pineal region), and for the brainstem and cerebellar vermis.

## Results

Table 1

Variable	Patient group (mean)			Control group (mean)
	Boys	Girls	Total	
Age (month)	45.21±12.99	41.41±13.69	44.07±13.15	44.97±12.95
Age of first symptoms (months)	23.07±6.99	21.58±5.48	22.62±6.54	
Age of diagnosis (month)	36.25±9.22	29.83±5.49	34.32±8.73	
Percentage of round head (%)	76.14±16.54	78.17±11.91	76.75±8.73	49.95±21.41
Frontal Lobe Size (Cc)	599.09±72.17	564.71±77.38	588.77±74.49	466.99±56.73
Amygdala volume (cc)	3.56±0.55	3.17±0.73	3.44±0.63	3.59±0.66
Total brain volume	1418.52±135.58	1398±99.01	1412.46±123.31	1183.04±123.42
Frontal volume ratio to total brain (%)	42.19±2.62	40.33±4.27	41.63±3.26	39.51±2.80
Amygdala Amount to Brain Total Amount (%)	0.25±0.038	0.230±0.054	0.24±0.044	0.300±0.039

### Age at the onset of symptoms and age of diagnosis

Age at the onset of autism symptoms was between 12 and 42 months with an average of  $6.54 \pm 22.62$  months. Age at the onset of symptoms in autistic boys was between 12 and 42 months with an average of  $6.99 \pm 23.07$  months and in autistic girls, between 16 and 36 months with average of  $5.48 \pm 21.58$  months.

Mann-Whitney nonparametric test revealed a statistically significant difference ( $p=0.422$ ) in average age at the onset of symptoms between girls and boys with autism.

Recent studies have shown that autistic boys and girls exhibit different behaviors so this could be the reason.

Age at diagnosis of autism was between 22 to 59 months with an average  $73.8 \pm 32.34$  months. Age of diagnosis of autism among boys realized to be 24 to 59 months with an average of  $9.22 \pm 36.25$  months and among girls, between 22 to 36 months with an average  $5.49 \pm 29.83$  months.

Comparison of average age at diagnosis between girls and boys with autism using the Mann-Whitney nonparametric test demonstrated a statistically significant difference between the two groups ( $p = .039$ ). On average, the age of diagnosis in girls was lower.

### History of prenatal problems

Out of the 40 patients, 26 patients (65%) had a history of prenatal complications. From among other patients, 2 patients (5%) had a history of neonatal jaundice, 1 patient (5.2%) of preterm birth, 2 patients (5%) of low Apgar score, three patients (5.7%) of labor problems and six others (15%) of several simultaneous problems.

In the control group, 32 out of 40 patients (80%) had a history of prenatal complications. From among the other patients, 5 cases (12.5%) had a history of neonatal jaundice, 2 cases (5%) of preterm birth, and one patient (2.5%) of low Apgar score at birth.

Comparing the two groups in terms of the history of peripartum problems using chi-square test showed a statistically significant difference between them ( $p = .021$ ).

### Family history

Out of the 40 patients, 10 patients (25%) had a family history of autism spectrum disorders, while in the control group, only 3 (7.5%) had a positive family history of autism spectrum disorders. A comparison between two groups in terms of family history of autism spectrum disorders using the chi-square test indicated a statistically significant difference between the two groups ( $p = .034$ ).

### Speech disorders and echolalia

In the group of patients, a total of 40 patients showed a range of speech disorders. 20 out of 40 patients (50%) suffered from echolalia. In the control group, 4 patients (10%) had a speech disorder that was associated with hearing impairment. None of the control group had echolalia.

Comparing the two groups in terms of speech disorders and echolalia using chi-square test showed a statistically significant difference ( $p < .001$ ).

### Head circumference

The investigation of the two groups in terms of head circumference percentiles showed that head circumference percentile was between 46 and 99 percentiles with an average of  $15.17 \pm 76.75$  percentile in the experimental group and between 12 to 96 percentiles with an average of  $21.41 \pm 49.95$  in the control group, respectively.

Independent t-test indicated that mean head circumference percentiles between the two groups was significantly different ( $p < .001$ ).

The mean head circumference percentile was equal to  $16.54 \pm 76.14$  and in the range of 46 to 99 and to  $11.91 \pm 78.17$  and in the range of 60 to 98 among autistic boys and girls, respectively.

Comparison of mean head circumference percentile of autistic girls and boys with autism using independent t-test showed a statistically significant difference ( $p = .704$ ).

As a result of the comparison of mean head circumference percentile between autistic and normal boys using independent t-test, it was found that there is a statistically significant difference between them ( $p < .001$ ).

Comparison of mean head circumference percentile among girls with autism and normal girls using independent t-test indicated a statistically significant difference ( $p < .001$ ).

### The amygdala

Investigation of the two groups in terms of the volume of the amygdala revealed that the volume of the amygdala was between 1.13 to 4.21 ml with an average of  $0.63 \pm 3.44$  ml in the experimental group and between 55.2 to 47.5 ml with an average of  $0.66 \pm 3.59$  ml in the control group.

Comparison of mean amygdala volume between the two groups using independent t-test showed a statistically significant difference between them ( $p = .322$ ).

The mean volume of the amygdala in autistic boys was  $0.55 \pm 3.56$  ml in the range of 1.23 to 4.21 ml and in autistic girls equal to  $0.73 \pm 3.17$  ml in the range of 1.13 to 3.70 ml.

Comparing the mean volume of amygdala between autistic girls and boys using Mann-Whitney test showed statistically significant difference between the two groups ( $p = .049$ ).

Comparing the mean volume of the amygdala between autistic patients with non-verbal disorder and other autistic patients using the Mann-Whitney test demonstrated a statistically significant difference between the two groups ( $p = .049$ ).

Mann-Whitney test showed that there was a statistically significant difference ( $p = .018$ ) in the mean volume of the amygdala between autistic patients with echolalia and other autistic patients.

Independent t-test revealed a statistically significant difference ( $p = .697$ ) in the mean volume of the amygdala between autistic and normal boys.

Comparison of the mean volume of the amygdala between autistic and normal girls using independent t-test showed a statistically significant difference between the two groups ( $p = .153$ ).

## Conclusion

From among the 40 patients, 25 patients had a history of convulsion. Among the other patients, 4 patients (10%) suffered from simple febrile convulsion (simple FC), 2 cases from complex febrile convulsion (complex FC), 6 cases (15%) from TCG and 3 ones (7.5%) from Landau-Kleffner syndrome (LKS). Of the 15 patients with a history of convulsion disorders, 5 patients (12.5%) used phenobarbital, 4 patients (10%) took valproate and 2 patients (5%) were treated with multi-drug regimen (4).

Only 8 cases (20%) of the 40 patients in the control group had complex FC. Of these, only one was using phenobarbital. Comparison between the two groups in terms of convulsion disorders using chi-square test showed a statistically significant difference between them ( $p < .001$ ) (5)

To our knowledge, the present retrospective study reports the largest series of systematic visual analyses of MRI from patients with non-syndromic AD. These patients have been carefully screened to exclude known medical disorders associated with autism. We observed an unexpectedly high prevalence of brain abnormalities (48%). This unexpectedly high level of anomalies contrasts with the generally accepted view that MRI is close to normal in children with AD [6]. This could be explained by methodological improvement, including here, of considering MRIs containing all the acquisitions necessary to detect brain abnormalities. We found three types of brain anomalies, including white matter hyperintensity on T2-FLAIR sequences, temporal lobe signal abnormalities and dilated Virchow-Robin spaces (7). Such abnormalities were not found in any child in the comparison group, which is in agreement with a recent MR study in a large group of normal children [8]. These abnormalities cannot be detected when only a T1 sequence is acquired. It is important to note that this high prevalence of abnormalities was found despite a stringent definition for an abnormal MRI. Indeed, all minor anomalies or normal variants (ventricular dilatation, accentuated Virchow-Robin spaces, abnormal hippocampal shape, arachnoid cysts, cerebellar atrophy, etc.) were not considered as abnormal. Similar results were found in a recent study that included a smaller sample of children with developmental disorders, including ASD, with abnormal MRI being reported in 49% of patients [9]. In addition, Taber et al. have also described high incidence of abnormal Virchow-Robin spaces in children and adolescents with ASD and normal IQ [10]. Our study was subject to a number of limitations. One intrinsic limitation is that the comparison group was not matched for IQ with the AD group, which was largely composed of children with AD and mental retardation. Therefore, we cannot say whether these MRI abnormalities are specific to autism. Nevertheless, in our series, the 23 patients with normal IQ had the same types of MRI abnormalities as did patients with AD and mental retardation. In idiopathic mentally retarded children, the most frequently reported MRI abnormalities are ventricular dilatation, arachnoid cysts, moderate subarachnoid space enlargement, cerebellar atrophy and/or cortical atrophy, partially opened septum

pellucidum and/or cavum vergae and corpus callosum anomalies [11]. These types of abnormalities are often considered to be minor MRI findings and were not reported as abnormal in the present study. Nevertheless, they were rarely observed in the AD group (3%). Another limitation is that our findings cannot be extended to persons with high-functioning AD or to the full spectrum of ASD, which covers very heterogeneous disorders. Therefore, further clinical MRI investigations are necessary in these sub-groups of patients. Finally, another important issue will be to further characterize putative clinico-radiological sub-groups in AD and future studies need to be performed. Certainly, the MRI abnormalities recognized in the present study are not specific to AD, since they have been previously reported in other neurological, metabolic or genetic childhood disorders. Posterior periventricular hyperintensity was found as a white matter signal abnormality in 18.77% of the patients. Classically, this abnormality can be found in periventricular leukomalacia, metabolic disorders, viral infections or vascular disorders [12]. White matter MRI abnormalities were recently described in a large series of patients with cerebral palsy and were categorized into three levels of severity from mild to severe; in this study the abnormalities were always linked to motor deficits [13]. The white matter abnormalities that we have found in children with autism are comparable to the mild to moderate levels described in cerebral palsy, but no motor deficits were observed in our AD patients. Isolated or associated white matter abnormalities were found in 30.77% children with autism in our series. They could represent injury to the brain parenchyma and resultant disruption of neural circuitry. The main question is which different mechanisms may be involved in the emergence of such white matter abnormalities (14). It is highly possible that these white matter hyperintensities (WMH) might simply represent the 'tip of the iceberg' in terms of structural white matter lesions. Thus, the presence and severity of white-matter hyperintensities associated with autism might be understood as an extreme consequence of underlying microstructural processes that affect brain connectivity and which may be more specifically investigated using diffusion tensor imaging methods. WMH, depending on the localization, are commonly classified as periventricular hyperintensities (PVH) or deep white matter hyperintensities (DWMH) (15). Deep white matter hyperintensities were identified as having mainly a vascular etiology, and periventricular hyperintensities could be due to ependymal loss, differing degrees of myelination and cerebral ischemia. WMH are reported to be commonly associated with older age, and cardiovascular risk factors such as hypertension and diabetes. Lesions in one specific part or disruption of interconnections among areas regulating social and communication cognition could trigger the onset of autistic symptoms. Furthermore, posterior white matter connections with the temporal regions could be of particular importance to social disturbances in autism. Although, we did not measure white matter connections, lesions in such neuroanatomic pathways may be causal factors of behavioral and emotional dysfunctions in autistic patients. Finally, it is also important to understand how WMH severity changes over time.

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