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Original article

Magnetic resonance imaging in autism spectrum disorders: clinical and neuroradiological phenotypes

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Abstract. *Background and aim:* Autism Spectrum Disorders (ASDs) are a group of neurodevelopmental disorders that can severely compromise social and cognitive functions in childhood. Magnetic Resonance Imaging (MRI) currently represents the gold standard as an in vivo and non-invasive study of the human brain morphology. This work aims to search for possible links between clinical phenotypes and radiological anomalies that may be relevant and pathognomonic in the subsequent diagnosis of ASDs. *Methods:* This is a retrospective study in which 132 patients (112 males and 20 females) with neurodevelopment disorders, including ASDs, were enrolled. The population study was divided into three groups considering their own pathological diagnosis. All patients included in this population underwent genetic screening and one or multiple 1.5T MRI scans were performed to evaluate potential anomalies of the corpus callosum, periventricular white matter, ventricular space, cerebellum, subarachnoid space and thalamus. *Results:* Univariate analysis showed that the presence of MRI brain abnormalities was a significant variable in predicting the presence of ASDs ($p<0.001$). Increased ventricular volume was one of the most replicated findings in ASDs patients (48% in group 3, 24% in group 1 and 4 % in group 2) and it was reported to be statistically significant both in uni- and multivariate analysis ($p<0.025$, $p<0.045$), resulting even as a potentially predictive factor of diagnosis. *Conclusions*: This study can represent a starting point for the research of new radiological evidence that might be important to early diagnose ASDs and for making a differential diagnosis with all those conditions that mimic autistic traits, but which are not clinically connected to the spectrum disorder itself. (www.actabiomedica.it)

Key words: Autism Spectrum Disorders (ASDs), Magnetic Resonance Imaging (MRI), neurodevelopment disorders, neuroradiological phenotype

Introduction

Autism spectrum disorders (ASDs) are a group of heterogeneous neurodevelopmental conditions, characterised by early onset difficulties in social communication and unusually restricted, repetitive behaviour and interests. Therefore, ASDs can severely disrupts social and cognitive functions (1, 2). The prevalence of autism is constantly increasing compared to the first epidemiological studies carried out (which had identified a prevalence of about 4,1/100.000 individuals). It could be explained by increased awareness of symptomatology of disorders and improved diagnostic techniques and classification standards (3). In fact, overall prevalence of ASDs is between 0.62-0.70% (3, 4). The male sex is generally the most affected with an incidence rate 2-3 times higher than the female patients (5-8). The aetiology of ASDs is still unknown, but genetic and environmental factors are probably involved. Indeed,

studies have supported the correlation between ASDs and genetic mutations, such as the NLGN3, NLGN4, SHANK3 genes, clinically related to language and neural communication (9-11). Hence the indication to carry out a genetic panel that includes the most widely known genetic variants expressed in the general population in the diagnostic algorithm of autism. In addition, alongside the multitude and heterogeneity of genetic mutations involved, there are factors that could be defined epigenetic or otherwise related to the environment. For example, the use of iatrogenic drugs during the gestational period, such as sodium valproate, commonly taken in the treatment of epilepsy, is related to a relative risk of developing autism of about 8 times greater in the new-child (12). Finally, ASDs diagnosis is made following criteria described in the DSM-V (Diagnostic and Statistical Manual of Mental Disorders – Vth edition) (Tab.1) (13).

The development of neuroimaging techniques has given rise to a considerable boost in the observation of both morphological changes in ASDs patients and changes in brain activation patterns typically related to some of the key symptoms of autism, such as eccentric behaviors, marked interest reduction and mental retardation (14). In particular, the use of Magnetic Resonance Imaging (MRI) has gradually acquired a leading role to conduct multiple studies both morphological and functional thanks to the high sensitivity, the quality of the images obtained and the absence of radiation. All these features make MRI techniques the ideal tool for research and studies involving children and adolescents (1). The first MRI studies of ASDs patients were conducted in the United States by Piven et al. in the early 1990s. These publications revealed that ASDs subjects brain had significant changes in the cerebellum, pons and ventricles (15). Currently, in the literature there are many studies that emphasize that the basis of ASDs can be numerous and various morphological and functional abnormalities of different brain areas are involved (1, 16-18). This work aims to search for possible links between clinical phenotypes and radiological anomalies that may be relevant and pathognomonic in the subsequent diagnosis of ASDs. The evidence of a relevant statistical correlation between these anomalies and the diagnosis of ASDs might be helpful to recognize earlier the clinical and radiological phenotypes implied in the development of the ASDs. Moreover, an early diagnosis might lead to a better approach to the management and treatment of the disorder, improving the quality of life of these patients.

Materials and methods

Data wereretrospectively collected, by a single operator, in a period between July 2018 and July 2021, from a database of patients with neurodevelopmental disorders in follow-up at the IRCCS "Casa Sollievo della Sofferenza" in San Giovanni Rotondo (FG). 132 patients (112 males and 20 females) were enrolled in this study. All included subjects performed blood sampling for genetic screening with karyotype,

Table 1. DSM-V Criteria for ASDs.

Symptom Criteria	Traits
Deficits in social communication and social interaction across multiple contexts	Deficits in social-emotional reciprocity; Deficits in nonverbal communication behaviors (e.g. gestures) used for social interaction; Deficits in the development, maintenance, and comprehension of relationships
Restricted, repetitive patterns of behavior, interests or activities	Stereotyped movements, speech, and use of objects; inflexibility to change of routines or ritualized patterns; Restricted interests with strong, abnormal attachment; Hypo- or hypersensitivity to environmental factors
Symptoms must be present in early developmental period	Symptoms may not manifest until social demands exceed limited capacities
Combination of symptoms significantly impair detail functioning	Level 3 – Requiring very substantial support Level 2 – Requiring substantial support Level 1 – Requiring support

Array-Comparative Genomic Hybridization (CGH-a) and Next-generation sequencing (NGS) panel for neurodevelopmental disorders. The primary objective of this study was to compare differences between 3 groups of patients in terms of anatomical and radiological abnormalities after one or multiple MRI scans in patients with neurodevelopmental disorders. Therefore, the population study was divided into three different groups, considering their primary diagnosis. Group 1 (n=83) entailed patients that met criteria for ASDs diagnosis. Group 2 (n= 26) consisted of patients with clinically mild neurodevelopmental disorders, excluding ASDs. These are selected patients, whom diagnosis was emotional disorders, mild intellectual disability, ADHD (Attention-Deficit/Hyperactivity Disorder), and language disorders. Any cognitive impairment was previously assessed through the application of neurological clinical and diagnostic assessment tools such as the use of verbal (WISC-IV) and non-verbal (LETTER III) IQ tests. Group 3 (n=23) included patients with ASDs diagnosis and other comorbidities. The dataset was not age- or gender-standardized and all the population study met the inclusion criteria. ASDs diagnosis was made using criteria validated in 2013 by the DSM-V (13). All the subjects whose diagnosis was in process, with twitches or spasms and with moderate-severe intellectual disability didn't meet the inclusion criteria. Patients who didn't have at least undergone an MRI scan of the brain and who did not receive a genetic investigation were excluded.

Imaging methods

All patients included underwent one or multiple 1.5T MRI scans (Philips Ingenia 1.5T). Imaging techniques such as ROI's (region-of-interest), SBM (surface-based morphometry) and VBM (voxel-based morphometry) were applied to specifically analyse the brain areas of interest.

Anomalies evaluated in brain MRI were morphological changes in term of shape and increase or reduction in volume of the specific brain area of interest and focal or diffuse abnormal signal intensities of brain tissue. White matter abnormalities were classified as multiple punctate or plaque-like confluent hypersignals on T2 and FLAIR sequences. These anomalies were considered at the level of corpus callosum, periventricular white matter, ventricular space, cerebellum, subarachnoid space and thalamus. Normal variants or minor abnormalities, such as posterior fossa cysts, abnormal hippocampal shape or minor cerebellar atrophy, were not considered as abnormalities and were classified as normal MRI.

Statistical features

The dataset was matched to a PS (propensity score) using age, sex, presence of morphological anomalies on brain MRI scans and presence of possible genetic mutations as possible variables, to check for potential confounding factors.After PS matching, the quality of the equilibrium of the covariables was checked through the evaluation of standardized differences. Continuous variables were reported as median and interquartile range and compared with the Mann-Whitney U test, while categorical variables were reported as rates and tested with Fisher's test or chi-square test. Finally, uni- and multivariable cox-regression analysis, involving the entire study cohort, was used to evaluate the predictive values for autism diagnosis. Statistical analyses were performed using Stata-SE 15 (StataCorp LP, College Station, TX, USA).All tests were 2-sided with a significance level set at $p < 0.05$.

Results

The statistical analysis of the collected data shows some significant evidence, schematically reported in Tables 2 and 3.

The difference between the 3 groups in terms of age was significant: the population affected by ASDs had an average age of about 6 years, just over half of the populations represented by groups 2 and 3. Male gender had shown significant differences among the three groups: the population with a ASDs diagnosis (group 1) was made up of more males (90%), with a percentage higher than the second (81%) and third group (70%). Conversely, the female subjects were distributed in a more heterogeneous way and without significant differences between the three groups,

Table 2. Multiparametric correlations with ASDs.

	Group 1 (n= 83)	Group 2 (n =26)	Group 3 (n=23)	p < 0.05
Age	6 (3, 9)	11 (7, 14)	11 (3, 13)	0.001
Sex, n (%)				
males	75 (90%)	21 (81%)	16 (70%)	0.039
females	8 (10%)	5 (19%)	7 (30%)	
Genetic abnormalities, n (%)				
absent	78 (94%)	24 (92%)	22 (96%)	0.9
Present	5 (6%)	2 (8%)	1 (4%)	
MRI abnormalities, n (%)				
absent	32 (39%)	20 (77%)	3 (13%)	< 0.0001
present	51 (61%)	6 (23%)	20 (87%)	
Corpus callosum abnormalities, n (%)				
absent	63 (76%)	24 (92%)	17 (74%)	0.2
present	14 (17%)	2 (8%)	6 (26%)	
Periventricular white matter abnormalities, n (%)				
absent	63 (76%)	23 (88%)	17 (74%)	0.4
present	20 (24%)	3 (12%)	6 (26%)	
Ventricular space abnormalities, n (%)				
absent	63 (76%)	25 (96%)	12 (52%)	0.002
present	20 (24%)	1 (4%)	11 (48%)	
Cerebellum abnormalities, n (%)				
absent	80 (96%)	25 (96%)	21 (91%)	0.6
present	3 (4%)	1 (4%)	2 (9%)	
Subarachnoid spaces abnormalities, n (%)				
absent	75 (90%)	26 (100%)	20 (87%)	0.2
present	8 (10%)	0 (0%)	3 (13%)	
Thalamic abnormalities, n (%)				
absent	75 (90%)	26 (100%)	22 (96%)	0.6
present	3 (4%)	0 (0%)	1 (4%)	

while being more represented in group 3. Focusing on morphologic alterations on MRI, there were statistically meaningful differences among the three groups, highlighted by the presence of a greater number of anomalies between the patients of groups 1 (61%) and 3 (87%), instead of group 2 (23%). Subsequently, the frequency of structural brain anomalies among the three groups was analyzed through MRI scans. Abnormalities concerning shape and size of the corpus callosum were found. However, these morphological anomalies were present with different frequencies in the three groups, with prevalence rates of 17% in group 1, 8% in group 2 and 26% in group 3. In addition to this, no significant differences were found in

Table 3. Predictive factors of ASDs. Univariate and multivariate analysis.

Covariables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P> |z|	OR	95% CI	P> |z|
Sex	0.69	0.23, 2.12	0.519	0.90	0.82, 0.99	0.029
MRI abnormalities						
absent						
present	6.76	2.49, 18.35	<0.001			
Corpus callosum abnormalities						
absent						
present	2.79	0.61, 12.79	0.186	1.64	0.32, 8.33	0.550
Periventricular white matter abnormalities						
absent						
present	2.49	0.69, 8.98	0.163	1.40	0.35, 5.55	0.632
Ventricular space abnormalities						
absent						
present	10.33	1.34, 79.64	0.025	7.62	0.96, 60.56	0.045
Cerebellum abnormalities						
absent						
present	1.24	0.14, 11.07	14.09	1.12	0.11, 11.42	0.922

the prevalence of periventricular white matter abnormalities (Fig. 1) among the three groups.

In fact, the latter was present with a frequency of 24%, 12% and 26% respectively in the three groups under examination. Other abnormalities in brain structures, such as those affecting the subarachnoid spaces and the thalamus, were not different as they did not fall within the established confidence interval. Nevertheless, these lesions were absent in the group of patients with minor neurodevelopmental diseases compared to the other two groups. Radiological anomalies, with proven significance between the three groups (thus falling within the confidence interval), were the ones concerning the ventricular space (Fig. 2): group 3 showed the greatest number of specific alterations (48%), group 1 population showed an alteration rate 2 times lower (24%) and in group 2 this difference was much more marked, as anomalies of the ventricular space occurred with a frequency six times lower (4%) compared to group 1 and twelve times lower compared to group 3.

Furthermore, univariate statistical analysis showed that presence of brain MRI anomalies was a significant variable in predicting ASDs and that increased ventricular volume was jointly significant in both univariate and multivariate statistical analyses.

Discussion

This neuroradiological study suggests possible correlations between morphological anomalies in different brain structures and the subsequent diagnosis of ASDs. MRI is confirmed as the gold standard to study brain structures, as a useful and non-invasive tool, highlighting alterations and contributing to the diagnosis of neurodevelopmental disorders. The subdivision of the population study into three groups was chosen in order to distinguish three different sub-categories of patients with well-defined characteristics: group 1 included only ASDs patients, group 2 included mild neurodevelopmental disorders, chosen in order to be

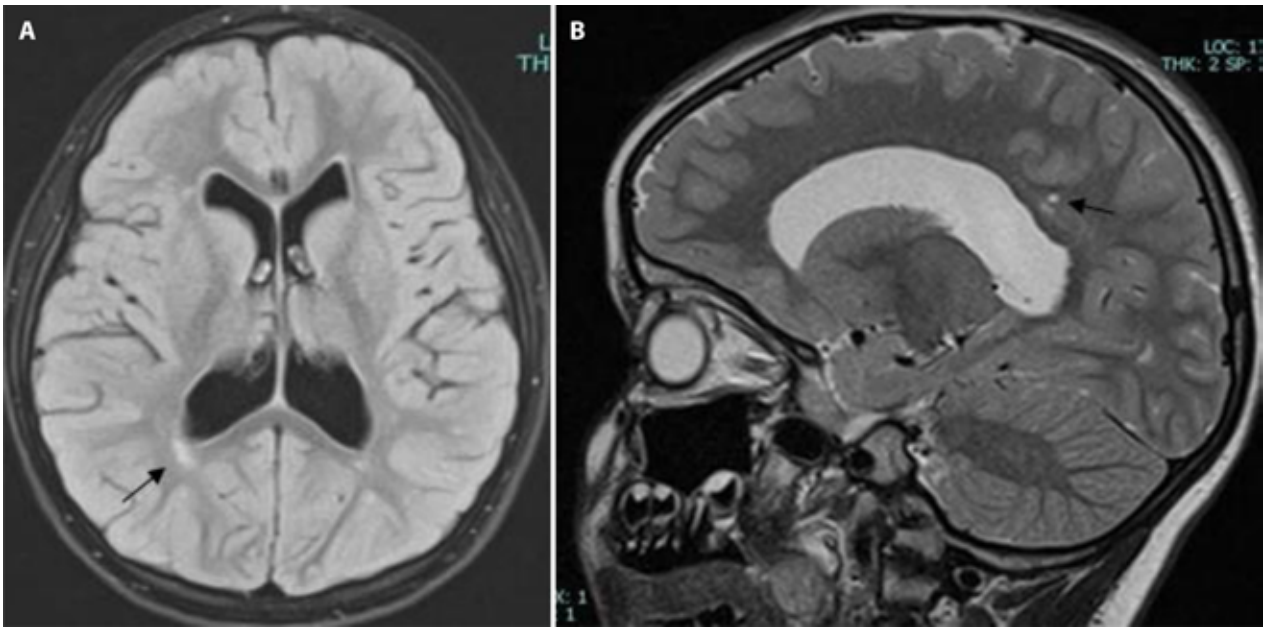

Figure 1. 6-year-old boy with ASDs diagnosis (Group 1). MRI Axial T2-FLAIR (A) and Sagittal T2-TSE (B) images show mild ventriculomegaly and periventricular white matter abnormalities (black arrows).

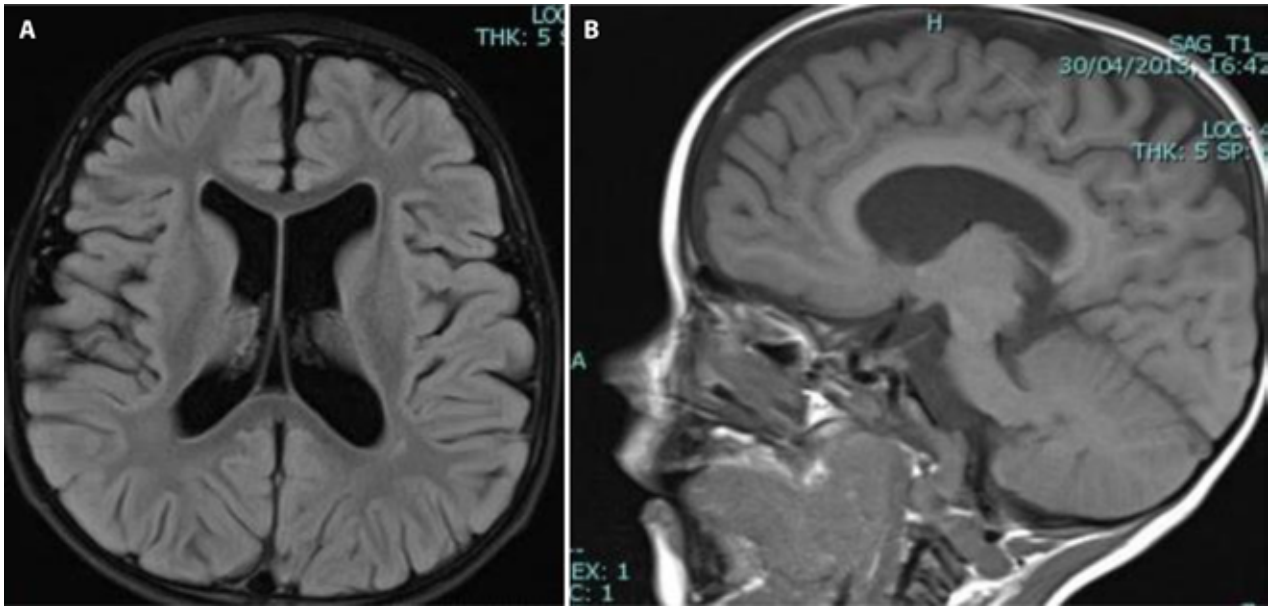

Figure 2. 7-year-old boy with ASDs diagnosis and psychomotor retardation (Group 3). MRI Axial T2-FLAIR (A) and Sagittal T2-TSE (B) images show moderate ventriculomegaly and enlargement of the subarachnoid spaces.

comparable to a healthy control group and group 3 represented a more heterogeneous group, including patients with ASDs and other comorbidities. The higher frequency of male in ASDs patients was in line with current epidemiological evidence (5-8). Unsurprisingly, a significant correlation between the presence of MRI anomalies and the diagnosis of ASDs was found, data already validated in literature (). These abnormalities,

however, were found in greater numbers in group 3 than in the other groups, in all the radiological subcategories examined. In fact, in our analysis, patients in group 3 had a greater presence of radiological alterations (87%) than the other two groups. This evidence is predictable, as group 3 included subjects who had already been diagnosed with ASDs but burdened by other neurodevelopmental disorders or known genetic variants. As for the morphological abnormalities of the cerebral ventricles, they were observed with a much higher cumulative frequency (and statistically relevant) in the subjects of groups 1 and 3 than in the subjects of group 2. This indicates how alterations at the level of the cerebral ventricles (often reported as mild or moderate ventriculomegaly) may be more frequently present in the real population with ASDs, than in the healthy population. The results are in line with numerous other similar studies in the literature, in consideration that the morphological anomalies at the level of the ventricular space are among the ASDs radiological findings with greater statistical number (2,2). In addition, this study was able to demonstrate how the presence of ventricular space abnormalities, can theoretically be used as a predictive factor of the development of ASDs in children under the age of 2 years, the minimum age to meet diagnostic criteria. Further scientific evidence confirming these results could in the future lead to an improvement of the diagnostic process and the therapeutic approach of the patient with ASDs.In our study, on the contrary, there is no significant correlation, in terms of predictivity, between the frequency of abnormalities at the level of other brain structures and the possible development of ASDs, as reported in literature (2-2).

The limitations of this work are attributable to the monocentric nature of the study; in fact, the possibility of collecting data in a single centre tends to reduce the sample size and statistical reliability. Moreover, since this is a retrospective study, one of the main limitations is certainly the lack of reliability compared to prospective counterparties. The sample size, while considered adequate considering the nature and epidemiology of the pathology, could be further increased in order to obtain greater statistical reliability. The absence of a diagnostic and radiological assessment on an annual basis and the limited time window in which the study was carried out (2018-2021) does not allow a wider view of the situation being studied but represents a "static" picture of a limited period of time. Finally, the study could acquire considerable value with complementary studies concerning functional MRI techniques and future MRI investigations should include well-characterized groups of autistic and matched healthy individuals.

Conclusion

The findings of this study are generally in line with data reported in the literature and at the same time represent a starting point for the search for new radiological evidence that may be important not only in order to make an early diagnosis of ASDs but also to make a differential diagnosis with all those conditions that can mimic autistic traits, but which are not clinically connected to the spectrum disorder itself. Further structural and functional MRI studies are desirable to collect more evidence that may support the findings obtained in this paper.

Abbreviations: ASDs: Autism Spectrum Disorders; DSM-V: Diagnostic and Statistical Manual of Mental Disorders – Vth edition; MRI: Magnetic Resonance Imaging; PS: Propensity Score

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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