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Research Article

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Medical Investigations in Autism Spectrum Disorders. A critical review of the everyday practice

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Abstract

Objectives: *To evaluate the outcome of medical examination in a population of children with autism spectrum disorders (ASD) and to describe its usefulness.*

Study design: *In this cross-sectional study, we evaluated the records of 122 patients with ASD to analyze their clinical course, medical investigation and outcomes.*

Results: *A total of 122 patients with ASD were included (0-18 years). Regarding the additional investigations, none of them has proved to have a high diagnostic yield in the absence of specific clinical features except from next generation sequencing (NGS), which showed a higher efficiency in comparison with the other genetic tests performed.*

Conclusions: *Clinical context should be the main determining factor for the execution of additional medical investigations in children with diagnosis of ASD. Nevertheless, given its high yield, NGS would be indicated from the beginning in children with ASD as part of the etiological diagnosis.*

Keywords: Autism spectrum disorder, medical conditions, comorbidity, next generation sequencing, epilepsy, children, neuroimaging.

Abbreviations:

ASD: Autism Spectrum Disorders;
NGS: Next Generation Sequencing;
DSM: Diagnostic and Statistical Manual of Mental Disorders;
NICE: National Institute for Health and Care Excellence;
AAP: American Academy of Pediatrics;
SD: Standard Deviation;
EEG: Electroencephalogram;
ABR: Auditory Brainstem Response;
MRI: Magnetic Resonance Imaging;
CMA: Chromosomal Microarray;
CNV: Copy Number Variant.

Introduction

Autism spectrum disorders (ASD) is a biologically based neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction and restricted, repetitive patterns of behavior, interests, and activities. The diagnosis of ASD is made clinically based on two sets of diagnostic criteria -the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Disease Classification (ICD) [1]. It is a very heterogeneous group regarding etiology, clinical phenotype, outcomes and comorbidities.

Nowadays it is recommended not routinely perform any medical investigation as part of the diagnostic assessment, but consider it based on clinical and physical examination [2]. Despite these recommendations and, probably, because of the heterogeneity of the disorder, it is not well established how extensive these medical investigations should be in every case of ASD, in the

search of etiology and common coexisting medical conditions. In addition, different guidelines do not agree with regard to genetic testing; while National Institute for health and care excellence (NICE) guideline advises to consult with the regional genetics center and perform genetic tests if there are dysmorphic features, congenital anomalies and/or evidence of an intellectual disability, the American academy of pediatrics (AAP) suggests performing a genetic evaluation in every case of ASD as some clinical studies have identified similar yield for genetic testing in children without any risk factor [2, 3].

Previous studies have described that about in 10% of the patients with ASD a concurrent medical disorder is found through these medical investigations [4-6]. However, even with these findings, the etiological relationship to ASD is often unclear and it usually does not change the management of the child. In addition, sometimes it is difficult to assess those symptoms and determine whether or not to perform a specific study in individual cases. It is frequent to find a great variability within different areas and hospitals that could be in part explained by the great heterogeneity in ASD and discrepancy between different protocols. Our purpose is to describe the outcome of routine medical examination in a population of children diagnosed with ASD.

Patients and Methods

Patients with a definitive diagnosis of ASD based on DSM-V criteria were included in the study. Physicians managing patients with ASD from Fundación Jiménez Díaz University Hospital (Madrid, Spain) participated in this study. Permission for retrospective data collection and data analysis was obtained from the respective institutional ethics committees.

Available medical records of all patients were reviewed. The following data were extracted: epidemiological data, family history, personal history, development milestones, neurological and general examination, anthropometrics, DSM-V severity levels, biomedical investigation -electroencephalogram (EEG), blood tests, neuroimaging, genetic tests, metabolic studies, sight and hearing evaluation-, outcomes of medical investigations and impact on patient's management.

Descriptive statistics were used. Data were summarized as percentage (%) or mean ± standard deviation (SD) as appropriate. For independent factors Student's t-test was used and association between quantitative and qualitative factors was carry out with Chi-square test.

Results

One hundred and twenty-two children were included, 18 girls and 104 boys, with a mean age 5.1 year at the time of diagnostic assessment (range 4.5 -5.6 year). Sample characteristics are described in Table 1.

Table 1: Clinical characteristics

Sample characteristics	N (%)
Sex Male Female	 104 (85.2) 18 (14.8)
Age (y): mean, range	5.1 (4.5-5.6)
Intellectual disability Intelligence Quotient (IQ) <70 Not studied	 12 69
DSM V severity level Level 1 Level 2 Level 3	 51 (41.8) 45 (36.9) 26 (21.3)
Developmental regression	10 (8.2)
Seizures	8 (6.5)
Psychiatric comorbidities	42 (34.4)
Obesity	21 (17.2)
Associated neurological symptoms	14 (11.5)
Dysmorphic features	27 (22.1)
Macrocephaly	3 (2.4)
Microcephaly	4 (3.2)
Dyschromia	28 (23%)

Birth related characteristics of 121 children were collected. Nearly 28% of the ASD cases were delivered by caesarean section, planned or emergency and 11% were born premature. In our sample, the most frequent psychiatric disorder associated was attention deficit hyperactivity disorder (42 patients, 34%). Café au lait spots were observed in 28 patients (23%) although only one child met criteria for neurofibromatosis. In total, 716 medical investigations were carried out, of which 45 (6.5%) showed abnormal results. However, of the 106 children with tests done, only in 9 patients (8.4%) those tests supposed a change in their management.

EEG was indicated in 75 children (61.4%), showing pathological findings 6 patients (8%) and impacting on treatment only in 2 children. Temporal lobe location of the epileptic activity was the most frequent. Reasons to indicate EEG and impact on management is described in figure 1. No association was found between EEG abnormalities and severity of ASD.

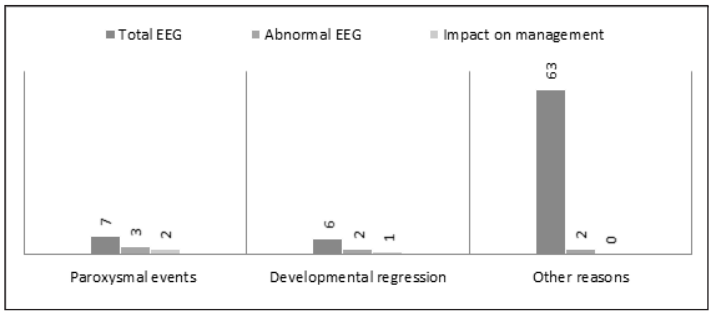

Figure 1: Reasons to indicate EEG and impact on management

In 60% of patients, exams of transaminases and thyroid function were carried out with no pathological findings. Also, celiac disease was studied in 65% of children with any positive result. Ammonium and lactate were measured in 32% of children with normal results in all of them. Other metabolic tests were performed in 5 patients with no positive results. Creatine kinasa (CK) was requested in 60 children (49.2%), with high values in 4 children. Of these 4 children only in one case there was an associated hypotonia. Hearing tests were performed in 48 children (39%), being auditory brainstem response (ABR) the most frequent test performed, all of them with normal results.

Abnormal findings on magnetic resonance imaging (MRI) were found in 9 of the 48 patients in which it had been solicited (18.8%), being white matter hyperintensities the most frequent finding (3 patients). There was significant correlation between abnormal finding in MRI and intellectual disability or seizures, separately ($p<0.05$). On the contrary, no association was found between abnormal finding in MRI and ASD severity. Spectroscopy was associated in 15 children (12%), with no significant results. Reasons to indicate MRI and impact on management is described in figure 2.

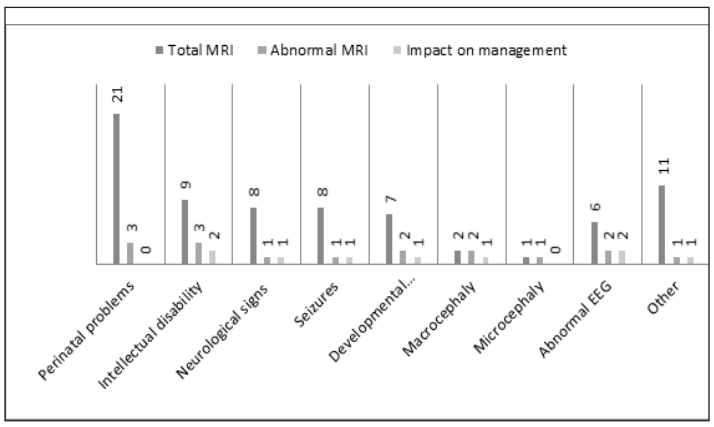

Figure 2: Reasons to indicate MRI and impact on management

Genetic study was performed in 66 children (54%), with remarkable findings in 26 (39.4%); of these, only 6 (9%) were considered as associated with ASD. All genetic findings were discussed with a specialist in clinical genetics. There was significant correlation between severity of ASD and genetic findings ($p<0.001$). The different genetic tests performed and its results are presented in Figure 3.

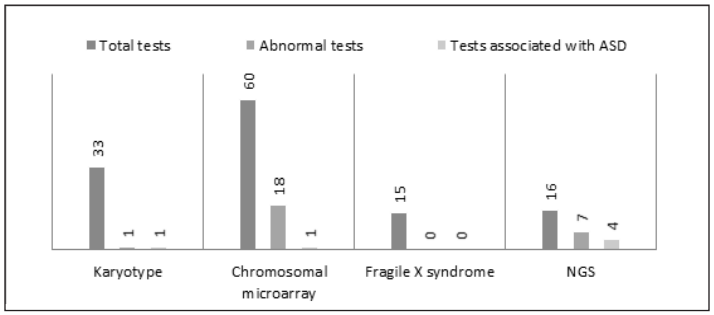

Figure 3: Genetic tests

Discussion

This study describes medical investigations and its results on a day-to-day basis, focusing on its usefulness. The main conclusion is that genetic tests are the more profitable studies for etiological searching, especially in those patients with severe ASD (as it has been previously described) [7]. Advances such chromosomal microarray (CMA) and NGS technologies have led to progress in the understanding of the complex etiopathogenesis of ASD. CMA is recommended if the etiology is not known and there is no specific feature that could lead to a concrete diagnosis (for example Rett syndrome or tuberous sclerosis). CMA reveals a definitively pathogenic copy number variant (CNV) in 5.4%-14% of cases, that could amount to 17-42% if CNVs of uncertain significance are included. Fragile X syndrome is not detected by CMA and, according to AAP; it should be excluded in any patient with ASD, accounting for approximately 0.45% of individuals with ASD. If both studies do not identify an etiology, NGS should be implemented (it has been reported 8-20% of diagnostic yields) [3]. Given the fast evolution of genetic testing all these recommendations are continuously updating. In addition, recent studies have pointed that high cognitive functioning ASD has a low diagnostic yield due to the challenge of distinguishing between rare variants unrelated to disease and those that are contributory [8]. Future protocols will probably distinguish between different groups of ASD but larger studies are necessary in order to better define this. In our study, since the sample is so small, we report only those findings that have previously been documented in larger studies. NGS has been the most profitable test (in line with other studies) whereas microarray has showed a low diagnostic yield as compared to other studies and no patient with fragile X or Angelman syndrome was identified (although it has been reported prevalence of 0.45-2% and 3.8%, respectively, in previous studies) [3, 4, 9]. Detecting a genetic etiology provides information about prognosis and may help to identify co-occurring medical conditions, avoiding unnecessary tests, so it should be a priority after a diagnosis of ASD [3, 10-13]. On the other hand, conducting EEG, MRI or laboratory tests showed little return in the absence of

other neurological symptoms.

Children with ASD have an increased risk for seizures [14, 15]. However, EEG it is not recommended as a routine evaluation except for cases showing seizures or atypical regression. It is common to find EEG abnormalities in absence of comorbid epilepsy that have been related to worse adaptive function but that in the every-day clinics would probably not change the management [3, 15]. Increased rates of epilepsy have been reported in ASD but prevalence varies significantly between different studies (5-46%) [14]. In this study only 8% of patients with EEG done showed pathological findings and of these, only two children needed a change in treatment what is consistent with previous recommendations.

Regarding standard MRI studies, it has been described temporal lobe abnormalities, hypoplasia of the cerebellar vermis, corpus callosum abnormalities…etc. but no consistent association between ASD and brain abnormalities have been detected and rarely it requires intervention [3, 4, 16]. Some of our patients showed abnormalities on MRI (18.8% of patients in who it had been solicited) and they were mostly unspecific, similar to other studies [3]. If MRI is considered its potential risks must be evaluated and balanced against the probability of diagnostic yields (especially in those patients who would need sedation to perform it). MRI may be indicated in patients with regression, micro-macrocephaly, seizures, intracranial manifestations of genetic disorders or other neurologic examination [3].

Metabolic testing shows a very low yield and it is not recommended in absence of associated neurological and general symptoms [3, 4, 17]. Our results support this statement: ammonium and lactate were studied in 32% of children with no abnormal results and in 5 patients a complete metabolic study was performed, guided by associated symptoms, with normal results in all of them. Classically it has been recommended to perform it in cases with regression, consanguinity, family history of early childhood dead, dysmorphic features and visual and hearing impairments although large population-based studies are lacking so accurate prevalence is not well established [3].

AAP recommends testing for CK in those patients with motor delay [3]. It remains unclear if it would be also interesting in cases without this motor delay (especially in infants) and some studies propose analyzing CK in patients with language delay or ASD symptoms as CK findings could guide genetic testing and an early diagnosis of neuromuscular disorders could lead to a better management of symptoms [18]. In our study, CK was requested in 60 children (49.2%), with high values in 4 children that are, currently, waiting for specific study. No conclusions can be made of this as we do not dispose of final results but larger studies are needed in order to better define if CK should be studied in all ASD cases.

NICE and AAP guidelines explain that children with language delay should have an evaluation of their hearing as part of their initial evaluation [2, 3]. It is well known the differences between ASD and deafness and it is accepted that hearing loss does not cause ASD. However, it remains unclear if hearing impairment contributes to ASD symptomatology and the clinical utility of auditory processing evaluations remains an area of study. In our sample, 39% of children were evaluated with no hearing loss detected, being ABR the most frequent test performed. Since higher prevalence of peripheral hearing dysfunction have been found when multiple measures derived from a complete audiological assessment are examined concurrently, it would be necessary to implement protocols to better define what kind of test should be implemented and its usefulness (performing only ABR could be relatively ineffective from a clinical perspective) [3, 19, 20].

Children with ASD have an increased risk of obesity and obesity-related metabolic disorders [21]. In this study, we have found 17.3% of obesity, similar to previous publications (18-22%) [21]. It should be implanted as part of the general evaluation in every child with ASD, which would allow to identify modifiable risk factors and easing access to active leisure. The main limitation of the study is that it is a retrospective study and its small sample size.

Conclusion

An appropriate clinical evaluation (focused on developmental regression, seizures, dysmorphic features and neurological signs) should guide the supplemental medical investigations in children with ASD. In searching for possible causes, genetic tests are the most efficient (taking into account that ASD severity and the presence of other signs would help in identifying those patients with a high yield in examinations).

It is needed to perform a critical analysis in every medical center that take care of children with ASD in order to avoid unnecessary tests that will not have any impact on management and, at the same time, try to find the cause and detect comorbidities that could impact on the daily performance. Variations in management between different medical teams lead to lack of confidence of families and a poor use of resources.

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