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ORIGINAL ARTICLE

Autism spectrum disorder: Clinical diagnosis and ADOS Test

Trastorno del espectro autista: Diagnóstico clínico y test ADOS

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Abstract

Introduction: Autism Spectrum Disorder (ASD) is a neurobiological disorder of high prevalence, whose clinical diagnosis is a constant challenge. **Objectives:** To describe the clinical profile in a cohort of children with ASD from referral to the specialist to a diagnostic test. **Patients and Method:** Descriptive study from the first symptoms perceived by the mother to the diagnostic confirmation of a series of 50 consecutive cases, which were clinically diagnosed with ASD between 2012 and 2016. Children aged between 3 to 10 years at the time of the ADOS-G test and language of at least one word were included. The children were evaluated neuropsychologically (functionality, intellectuality and ADOS test). We compared the median age to the neurological diagnosis, according to the autistic symptomatology and cognitive level. **Results:** The ADOS test corroborated an ASD in 44 children (88%), 93.1% were males. The average age at clinical diagnosis and ADOS test was 48.2 ± 19.3 and 62.6 ± 23.3 months. The neurological consultation in 72% of cases was parental/educator initiative due to symptoms such as social interaction disorder and language delay. The autistic symptomatology was mild, moderate and severe in 34.1, 47.7 and 18.2% respectively. In five of 27 children who were neuropsychologically evaluated cognitive deficits were detected. The median age at diagnosis was significantly lower in children with severe autism symptoms vs the ones with mild-moderate symptoms (p-value 0.024). **Conclusion:** Autistic symptoms determine the early consultation; therefore, it is necessary to guide the general and educational population as well as health professionals regarding these symptoms.

Keywords:
Autism; Autism Spectrum Disorders; ADOS test; K-BIT; WISC IV; Vineland Scale

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Introduction

In recent years, the diagnostic criteria for autism spectrum disorder (ASD) have changed, addressing the challenge associated with the high clinical variability of this condition. The DSM-V (Diagnostic and Statistical Manual of Mental Disorders) defines ASD as a persistent and heterogeneous neurodevelopmental disorder and categorizes the symptoms into two groups: a) deficiencies in communication and social interaction, and b) patterns of restrictive and repetitive behavior. Included in this spectrum are Asperger syndrome, Childhood disintegrative disorder, and Pervasive developmental disorder not otherwise specified[1].

In 2012, as reported by 11 ASD monitoring sites in the USA, the prevalence was 14.6 per 1.000 8-year-olds children (1 in 68), with a 4.5:1 ratio for males[2]. The prevalence has been increasing in recent decades, making it the second most frequent developmental disability, after intellectual disability[3,4].

One of the most widely used tools for the ASD diagnosis is the ADOS (Autism Diagnostic Observation Schedule) test, initiated in the 1980s[5,6]. The ADOS-G (generic) is a standardized, semi-structured assessment of social interaction, communication, imaginative play, and use of materials for children, youth, and adults who may have an ASD. It has four modules, each with diagnostic algorithms that allow the examiner to observe the behavior at different levels of development and language[7]. This instrument is sensitive and specific and the latest version available in Spanish is the ADOS-2, which includes improvements and novelties such as the design of a module for young children (12-30 months) called Module T, as well as the revision of the algorithms of modules 1-3[8].

Given the continuous development in the specific criteria of ASD, its relationship with prevalence and other clinical characteristics (gender bias, age of diagnosis, etc.), a detailed description of the autistic phenotype heterogeneity in our population is relevant.

The objective of our study is to describe the clinical profile in a cohort of children with ASD, from referral to a specialist to the ADOS-G test that will support such diagnosis. The processes will be described, from the first symptoms observed by the mother to the diagnostic confirmation.

Patients and Method

This study was carried out in the Pediatric Neurology Unit of the PUC (Pontificia Universidad Católica de Chile) between 2012 and 2016. It is a descriptive study of a series of consecutive cases that are clinically diagnosed (neurological examination and ADOS-G test). The clinical diagnosis of ASD was made by a pediatric neurologist according to DSM-IV criteria and was later referred to neuropsychological evaluation for functional and intellectual evaluation, and ADOS-G test.

The medical history and data such as sex, perinatal and family history, first symptoms of ASD observed by the mother, age at the time of consultation with a pediatric neurologist, reason for consultation, who referred to specialist, comorbidities, schooling, and requested studies were obtained from the clinical records. All children with suspected autism were referred to multidisciplinary rehabilitation or social skills workshops, and studies were requested during their subsequent check-ups. A school report was issued for integration or curricular adjustments. The study was approved by the Institutional Ethics Committee.

Admission criteria: First consultation on ASD suspicion and compatible ADOS-G, age between 3 and 10 years at the time of the ADOS-G test, and being able to speak with at least one meaningful word. Exclusion criteria: Vocalizations in which no words or approximation to words are recognized, carrier of a known genetic chromosomal disorder or severe malformation or structural damage of the central nervous system.

The neuropsychological assessment consisted of measuring adaptive and cognitive behavior with the Vineland Adaptive Behavior Scales Survey Form: 1-100), Kaufman Brief Intelligence (K-BIT), which provides IQ (M = 100, SD = 15), for total verbal and non-verbal IQ and Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV), applicable to children and adolescents aged between 6 years 0 months to 16 years 11 months, which also give IQ of the same types described above[10].

The ADOS-G test evaluated whether or not patients had autism spectrum symptomatology, and was categorized into a mild, moderate or severe symptomatic burden.

The neuropsychological evaluation was performed by a neuropsychologist with certification in ADOS test evaluation.

Statistical analysis

Categorical demographic variables were calculated in number and percentage, and for numeric variables, averages and standard deviation (SD) or medians and interquartile range (IQR) were calculated according to whether they distributed normal or not. The median age and IQR comparison at the onset of symptoms (reported by the mother), at the time of neurological consultation and ADOS-G test vs severity of autistic symptomatology, was carried out with the Mann-Whitney U test dichotomized in mild-moderate v/s severe ($p < 0.05$).

Results

Out of the 50 assessed children, 44 met inclusion criteria because they had a concordant ADOS-G. These 44 cases are described according to protocol (Figure 1).

93.2% (41/44) were boys, with a 13.6/1 boy: girl ratio. The average age at neurological evaluation and application of the ADOS-G test was 48.2 (± 18.3) and 62.6 (± 23.3) months. In 4/44 children there was a family history of ASD and 13/44 had perinatal morbidity (table 1).

The main requests for a first neurological evaluation in the 44 children occurred by spontaneous consultation of the parents in 18/44 and at the request of the educational institution in 16/44. Other requests were referred by another doctor (7/44 children) and by another health professional (psychologist, and speech and hearing therapist) in 3/44.

In the anamnesis of the 44 cases, mothers reported having perceived some neurodevelopmental alteration (first symptom), at an average age of 26.23 months (SD 14.0). Of this symptomatology, the language alterations and alterations in social interaction corresponded to 26/40 and 17/40 respectively. In 6/40 cases, a regression with language and social interaction loss was described. In the remaining cases (4 cases), they reported that they were 'always' different, without defining the main symptom.

Among the requested and performed tests, the hearing function was evaluated in 17/44 children (with normal auditory evoked potentials, audiometry, and impedance audiometry in 16/17, only 1 case with mild conductive hearing loss). In 15/44 cases (34.1%) the standard EEG was requested, where 3 out of 15 were abnormal, 2 with epileptiform activity, and 1 with a focal slowing. Other requested examinations were neuroimaging, genetic studies (karyotype, array CGH, molecular testing for fragile X), and metabolic studies, but most were not performed.

The neuropsychological evaluation was performed on 37/44 children. Adaptive behavior assessment (Vineland) was carried out in 10 children, and in 27 cognitive assessments (19 with K-BIT and 8 with WISC-IV). The Vineland evaluation had a median of 52 points (range 20-97). The results of the 27 children who underwent cognitive assessment were an 85 (58-126) verbal scale median, an 82 (52-119) executive scale, and a total of 83 (44-126) were obtained. An IQ of less than 70 (cognitive deficit) was detected in 5 children.

The ADOS-G test defined a mild to moderate autism symptomatic burden in 36 children (81.8%) v/s 8 (18.2%) with severe autistic symptomatology, and there were significant differences between median ages in both groups at the first neurological consultation (p 0.024) (Table 2).

Other detected comorbidities, besides cognitive deficit, were learning disorder in 27/44 (61.4%), sleep disorder in 14/44 (31.8%), eating disorder in 12/44

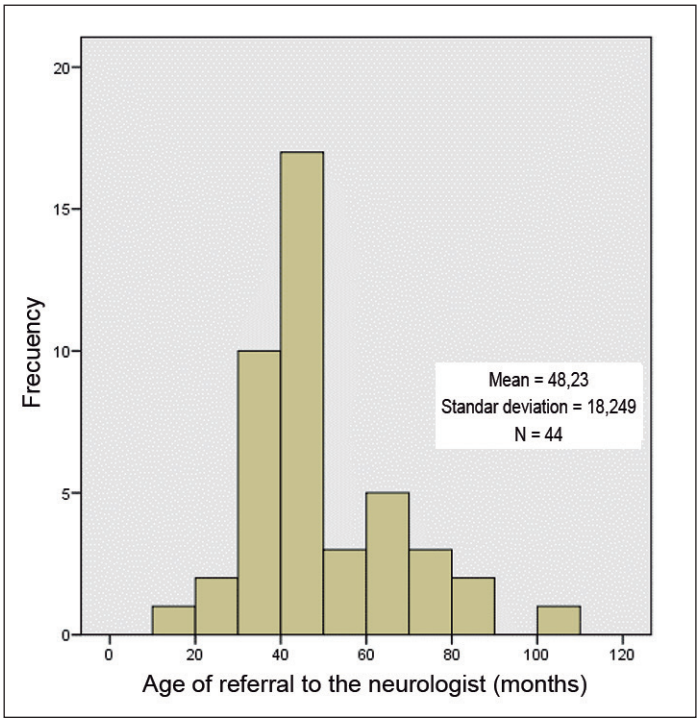

Figure 1. Age of referral to the neurologist / psychiatrist in 44 children with autism spectrum disorder (months).

Table 1. Clinical characteristics of 44 children with ASD evaluated between 2012-2017, PUC, Santiago, Chile

Characteristic	n (%)
Male gender, no.(%)	41 (93,2)
Age 1st query by ASD (months) average, SD	48,2 (±19,3)
Family history with ASD,no.(%)	4 (9,1)
Perinatal history (42/44),no.(%)	13 (31)
Prematurity,no.(%)	3 (7,1)
Hyperbilirubinemia,no.(%)	3 (7,1)
Acute fetal distress,no.(%)	2 (4,8)
Macrosomia,no.(%)	2 (4,8)
Other (HDP, PDNI, TT)no.(%)	3 (7,1)
Comorbilities	
Language Delay, no.(%)	38 (86,4)
Learning Difficulties, no.(%)	27 (61,4)
Sleep disorder, no.(%)	14 (31,8)
Eating disorder, no.(%)	12 (27,3)
Delayed motor development, no.(%)	6 (23,1)
Intellectual Disability (26), no.(%)	8 (18,2)
Epilepsy, no.(%)	3 (6,8)

HDP: hipertensive disorder of pregnancy; PDNI: premature detachment of the normally inserted placenta; TT: transient tachypnea.

Table 2. Comparison of median age at the detection of symptoms, clinical neurological diagnosis and ADOS test and functional and intellectual level v/s autistic symptom burden, in children with ASD, 2012-2016 years, Universidad Católica, Santiago, Chile

	Burden autism symptom		
Age (months)	Severe (8/44)	Mild-Moderate (36/44)	Valor p
Detection of symptoms according to the mother, median, (IR)	18.2 (20)	24.1 (16.5)	0.15
Diagnosis by neurologist, median, (IR)	36 (14,7)	44.5 (24.7)	0.024
Age at ADOS test, median, (IR)	51.5 (20)	60.3 (33.5)	0.06
	Nivel Intelectual y funcional		
	≤ 70 (n = 10)	≥ 71 (n = 27)	
Referral to neurologist, median, IR	56.5 (35.3)	60.1 (30)	0,21

IR: Interquartile range. ASD: Autism spectrum disorders.

(27.3%), motor developmental delay in 8/44 (18.2%), and epilepsy in 3/44 (6.8%).

In 27/44 cases, children attended kindergarten or school with integration and 10 of them also attended to speech-language programs. In 13/44 cases, they only attended a speech-language program or special education school (10 and 3 children respectively), and 4/44 were not in school.

Regarding drug therapy, 12/44 received melatonin, risperidone, methylphenidate or sertraline, alone or in combination, and antiepileptic drugs. Three children attended alternative equine therapy.

The 6 children whose ADOS results did not meet ASD criteria were not analyzed in this sample but were in followed-up for at least one year and their diagnoses were selective mutism and social anxiety disorder (2/6), intellectual disability (2/6), and cognitive disharmony and social anxiety disorder (2/6).

Discussion

The family and social impact of the ASD diagnosis, associated with the heterogeneity of its symptoms and the lack of biological markers, requires a multidisciplinary evaluation that allows us a high diagnostic certainty. A diagnostic error implies avoidable emotional and social costs. According to some authors[5,9], the misdiagnosis percentage with a clinical examination is 10-12%. In our work, there were 6/50 (12%) children whose ADOS test excluded an ASD despite having some similar behaviors and whose long-term follow-up was compatible with it.

Our cohort excluded children with a known chromosomal disorder, malformation, or severe brain damage and included children with developed oral language (at least one word or gesture with meaning), so we believe that an ASD subgroup with greater cognitive abilities, defined as high-functioning autism (HFA)[10,11] was selected. Although the admission criterion was age between 36 months and 10 years, we believe that the age at diagnosis of HFA is higher than the general population with ASD reported by Nassar and Daniels[12,13] and higher than the 18-24 months recommended for M-CHAT screening[14]. Therefore, it is necessary to assess the symptoms caused by the environment surrounding the child (parents and educators) who is highly sensitive to developmental alterations.

The surprising male predominance found in our boys (13.6/1 vs 4/1 or 7/1 for typical ASD and HFA) leads us to hypothesize that we have an underdiagnosis of HFA in girls[15,16]. There is growing evidence of a camouflage effect among girls with ASD, particularly those without intellectual disabilities, which may affect performance on standard diagnostic measures. One of the hypotheses of Head et al.[17] is that girls with HFA retain the complex social and emotional skills that characterize the female population because they use cognitive skills to respond to social situations[18]. Another theory is the 'female protective effect' since women would have a higher genetic threshold compared with men. Higher testosterone levels have also been found in girls with ASD than in girls with normal development[19].

The most frequent cause of consultation was the lack of social interaction (43%), a key element for ASD diagnosis. Language impairment or atypical language development is not a diagnostic criterion for ASD[1], but it is described in 86.4% of our patients. On the other hand, repetitive behaviors and restricted behavioral patterns were not mentioned as a cause of consultation, even though they were mentioned in the anamnesis during the neurological consultation and the ADOS test. This symptom must be specifically addressed in all consultations due to language alteration.

Regarding the diagnostic process times, 1 in 4 mothers described developmental alterations before

one year of age, but consultation or referral to a specialist occurred 20 months later. This is consistent with Ozonoff and Martin data[20,21] who indicate that autism can be diagnosed in infants, based on the parent's report and yet the median age at diagnosis is 4 years[22].

Intellectual disability is described in 42% of the population with ASD[16] and in our cohort, it was present in 5 of 27 children evaluated with K-BIT and WISC (Table 2). There was no significant correlation between IQ level and the median age at the time of neurological consultation, contrary to what occurred with the severity of ASD symptomatology. Children with severe autistic symptomatology consulted before children with mild-moderate symptomatology.

ASD may represent the final expression of several etiological factors including genetic conditions with known inheritance (e.g. tuberous sclerosis), metabolic diseases (e.g. phenylketonuria), congenital infections (e.g. congenital rubella syndrome), structural abnormalities (e.g. hydrocephalus, agenesis of corpus callosum) or neuroanatomical, and biochemical abnormalities.

In order to search for these etiologies, an exhaustive neurological-psychiatric clinical examination is essential and to assess the timing of appropriate neurophysiological, imaging, genetic, and metabolic studies. In most cases, these are very expensive and require sedation or general anesthesia in the case of neurophysiological studies and brain imaging which further limits their application. In our cases, a large number of studies were requested, most of which were not performed.

The genetic study is one of the most suggested in all cohorts of children with autism at an international level, specifically needed for genetic counseling in case of inherited etiologies[23]. In case of regressive autism or epilepsy suspicion, a sleep and awake EEG should exclude a Landau-Kleffner syndrome or encephalopathy with continuous spike and wave during sleep or another type of epilepsy that impairs communication, susceptible to improvement with antiepileptic drugs[24]. Neuroimaging or metabolic studies will be requested in case of high suspicion of a brain lesion or inborn error of metabolism.

The most frequent comorbidities were learning difficulties, and sleep and eating disorders (61.4%, 31.8%, and 27.3% respectively). Therefore, the most indicated drugs were methylphenidate and melatonin, highlighting little use of risperidone[17].

Although 40/44 children (90.1%) were attending an educational institution (kindergarten, regular school, speech-language programs, special education school) about 10% (4/44) remained out of school. No child attended behavioral-educational intervention therapies such as ABA (applied behavior analysis) considering the good results described in the literature[25] in programs started early and implemented intensively (more than 20 hours per week). There is a shortage of Chilean centers that perform this type of therapy (author's personal comment).

Among the weaknesses of our work are the admission criteria that biased the sample towards older children, with developed oral language and therefore better cognitive level. We did not include younger children because the autism symptomatic burden (ADOS-G) and intellectuality (K-BIT and WISC) assessment instruments are applicable in children over three years of age and children with developed oral language. We believe it is necessary to carry out new studies that include a sample with more and younger children (preschoolers) to be evaluated with current instruments such as ADOS-2, module T for children from 12 to 36 months and psychological tests such as the Leiter-R test (which allows us to evaluate intellectuality in children without oral language).

Conclusions

The autism symptomatic burden, given by alterations in interaction, communication, and restricted interests is the cause that motivates early consultation in parents and educators. Although there are clinical criteria defined in DSM IV and DSM V, clinically detectable, the high phenotypic variability of ASD related to autism symptomatic burden, cognitive capacity, and language requires teamwork (family, educators, and health care team) for early detection[26].

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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