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Sensitivity and specificity of a 3-item direct observation test for the early detection of infantile autism

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Abstract
Introduction: Early diagnosis of autistic spectrum disorder is difficult. The use of an observational test that focuses on the "core" clinical features of autism spectrum disorder with good sensitivity and specificity and that is within the reach of the first contact physician, pediatricians or even non-medical staff would help to detect the disorder and initiate the process of diagnosis and early therapeutic measures. Objectives: To determine the sensitivity and specificity of a 3-item direct observation test (TOD3) for the detection of autism in preschool children. Methods: Two groups were formed by convenience: Group 1, formed by 25 subjects with autism by DSM-5 or by ADOS-2. And Group 2, 25 healthy subjects with no history related to ASD and absence of neurological symptoms. MCHAT-ES, 3-items test (TOD3) and ADOS-2 were applied. Results: The direct observation test of 3 items obtained a sensitivity of 92% and specificity of 100% with a positive predictive value (PPV) of 100% and a negative predictive value (NPV) of 88%. The positive likelihood ratio (+ LR) was tending to infinity and the negative (-LR) was 0.08.
Conclusions: The 3-items direct observation test has good sensitivity and highly specific specificity for easy access and application detection of autism. It can be a useful clinical instrument for the pediatrician or first contact physician.

Keywords: Autism, Early detection. Screening. Autism Spectrum Disorder

1. Introduction

Autism spectrum disorder (ASD) covers a symptomatic constellation, affecting two major components of neurodevelopment: communication and social interactivity. It also has the trait of restricted patterns, inflexibility and constant repeating of activities and behavior. The first ASD symptoms can be observed before 3 years of age [1]. Centers for Disease Control and Prevention (CDC) in the USA reports a prevalence of ASD of 1/68 children [2]. In Mexico, the prevalence is 1 in 500 newborns [3]. The Mexican Autism Clinic estimated the prevalence of 1:150; 0.87% (95% CI 0.62, 1.1%) on a screening survey developed in grade-schoolers in the city of León, Guanajuato [4]. The American Academy of Pediatrics recommends that every child should be screened to detect issues related to neurodevelopment on regular well-child visits [5]. In Mexico, as a national screening and surveillance strategy regarding neurodevelopment, a screening test named EDI was considered [6,7]. This test is for children from 0 to 5 years of age with risk factors and with red flags or equivocal facts on neurodevelopment. It is important to clarify that this test is not specific for the screening of ASD. Pinar, Ozgur, and Kerim [8] developed a screening instrument of 3 items, named TOD3. This test is purely observational, easy and fast in its application (5 minutes). It has a sensitivity of 95% and a specificity of 85%. The objectives of this study were to obtain the sensitivity, specificity, and predictive values of TOD3 in preschool children using the Mchat-Es test (Modified Checklist for Autism Spectrum Disorder in Toddler, Spanish Version) as a screening standard [9], there is a modified version of Chat (Checklist for Autism in Toddlers) developed to improve its sensitivity and specificity being the original a 38%. Mchat´s sensitivity generally flows between 87% to 97%, nonetheless, the younger the study subject is (<24 months), sensitivity could fall to 75%. The specificity of mchat varies between 36% to 80%, with a time of application of 5-15 minutes total. The ados-2 (autism diagnostic observation schedule-2) test is the actual gold standard for the diagnosis of asd[10], which is why it was applied in this study. A brochure was designed and given with the description of the TOD3 test in order to be applied by pediatricians and primary care physicians to screen ASD in a timely manner**.**

2. Materials and methods

This is a prospective, observational study. Our hypothesis is that TOD3 has sufficiently high sensitivity and specificity (>90% y >85, respectively), to detect ASD in an early manner. This study was developed on a preschooler population in the city of Monterrey, Nuevo León, Mexico. 50 subjects, male and female, were invited to participate. The age range was between 18 and 47 months of age. The series was established by convenience in private practice centers (Neuropsychology (1), Pediatric Psychiatry (1), Pediatric Neurology (4)) in the city of Monterrey,

Nuevo León, México. Exclusion criteria for both groups were the presence of diseases like deafness, blindness, genetic diseases, cerebral palsy, or any other neurologic disease that could affect the results of the tests applied. Neurotypical cases were recruited from a daycare center related to our institution. 25 patients with clinical criteria for ASD according to DSM-5 and 25 patients without neurological complaints or previous family history for ASD were recruited. The selection of patients was made between July and August 2017 with approval by the ethics and investigation committee from our school (Instituto Tecnológico y de Estudios Superiores de Monterrey). A consent letter was signed by the parents in all patients.

2.1 Group cases

Group 1

Diagnosis of ASD by clinical history, DSM-5 or neuropsychological tests.

Group 2

Absence of ASD or neurologic disease.

2.2. TOD3 application

Tod3 of Pinar and Ozgur, with permission from the author, was translated to the Spanish language and adapted by the authors of this study (Available by request to the author). A committee of experts decided that the translation was adequate and gave the authorization to apply the test in this study. It is an observational test with 3 items that are scored as 0, 1 and 2 in items 1 and 2, and 0 and 1 in item 3. If the patient has 1 or more items with 1 or 2 points it means that he or she is at risk for ASD. If the patient gets 0 points on all 3 items, then he or she is considered riskless for ASD. Before starting the TOD3 test we need to know the patient´s name and nickname and put 1 to 3 showy toys, that do not emit any sound or light within the patient's visual field, no more than 2 meters of distance. A calm and audible, but not threatening voice is required for the verbal commands. One of the researchers developed the patient´s history of checking inclusion and exclusion criteria. Another researcher applied the MCHAT-ES test. This test is a survey type test composed of 23 items with yes/no answers. The questions are asked directly to the primary caregivers. MCHAT results were codified as follows: for 2 or more positive critical items and/or 3 or more non-critical items that are still positive for autism, the patient was considered as high risk. Tod3 results were codified as follows: for 1 or more positive items the patient was considered “at-risk”, while a score of 0 was considered “no risk”. Posteriorly, the ADOS-2 test was applied by the neuropsychology department, module T or 1 according to age, in a blind modality.

2.3. Statistics analysis

The measure of central tendency was obtained, dispersion and analytic tests of the variables with ANOVA for the age variable and the chi-square test for sex, economic level, results of TOD3, MCHAT-ES and ADOS-2 (see addendum table 2, operational definition of the variables). Sensitivity, specificity, positive and negative predictive value were obtained. BioStat® from AnalystSoft, Excel® from Microsoft, and SPSS® v20.0 from IBM were used. The sample size was adjusted to out possibility of the ADOS-2 test on 50 patients. A p-value of <0.05 was considered statistically significant for the comparison of all variables.

3. Results & Discussion

3.1. Results

58 participants were evaluated, 8 were excluded for having a neurological disease. The sample was 50 patients. The mean age for this sample was of 31.8 months (SD ±8.82) with a range of 18 to 47 months. Sex distribution was as follows: 33 males (66%) and 17 females (34%). Economic levels were distributed as follows: A/B level (2%), C level (30%), C+ level (64%), D+ and E levels (2%) respectively (11). The general traits of groups 1 (ASD group) and 2 (control group) are shown in Table 1; p values reflect the differences between age, sex, and economic level variables in subjects with positivity on the M-CHAT-ES and Tod3 test, being only statistically significative in the sex variable. MCHAT-ES test used to screen of ASD risk in group 1 showed 100% for high risk. In group 2, 16% were considered as high risk and 84% were considered low risk. In the TOD-3 test, group 1 obtained a high-risk score in 100% of the patients. Group 2 had 0% risk for ASD. The global predictive value was obtained for both MCHAT-ES and TOD-3 Table 2. ADOS-2 test was considered in this study as the gold standard for the diagnosis of ASD. The comparative results between MCHAT-ES and TOD3 show in Table 3.

3.2. Discussion

This study exposes some weaknesses since the sample size was very small due to the limitation of financing. We consider this study as a pilot study and not as a validation test (TOD3). Lower ages made measurements of sensitivity and specificity difficult. The sample was not stratified by age ranges because these subgroups were very small, and it would increase the chance of having statistical errors. Addressing the impact on age in the results of the tests, we can conclude that the results, even though they showed no statistically significant differences, should be kept as a reserve because we are counting with a small sample size. For some authors, the presence of cases considered by DSM-IV as non-specific tends to increase the rate of false negatives. For this study, the criteria from DSM-V were used, in which the cases are included in the sample without differentiating them. With this study, it is not possible to transfer and apply the results to the general population without validation studies for TOD3. It should be considered that the applications of TOD3 were made by ASD trained personnel, which is one of the objectives that untrained personnel can apply the test. The application of the test on the general population is required due to ASD´s low prevalence and this could influence positive and negative predictive values. It is necessary to amplify this research to include more patients and other nuclear manifestations of ASD to improve the general sensitivity of the test and apply the validation studies. Detection and confirmatory diagnosis of ASD carry some problems[12] and have acquired major importance due to the existence of specific therapies that could be applied in a timely manner y improve the long term evolution of these patients. A good screening method should be available in all health facilities. Pinar´s original study proposes that direct observation of the interactive component of interaction could be more sensible and specific than the scales answered by parents, and the results

proved this. Previous studies [13,14,15] have shown that social interactivity issues arise earlier and are more specific than the ones originated by language issues. Attention deficit can be observed very early in children with ASD [16,17,18]. Declarative pointing emerges between 12 and 14 months of age and is clearly associated with language development [19]. The correct following of instructions given by parents appears between 10 and 12 months. Responding to his or her name at 8 to 10 months is a constant, besides the development of a communicative and clear visual contact [20]. TOD3 showed an acceptable sensitivity (92%) and specificity (100%) as a screening test for ASD, being mainly highly specific. It can be a useful extension instrument of MCHAT. TOD3 has the advantage of not requiring special material or certified training for its application. It requires 5 to 7 minutes which is adapted best to the times of medical visits in public health services. TOD3 is a worthy tool in daily medical visits (mainly pediatricians) or useful for non-medical personnel for early detection of ASD.

4.0 Conflict of interest's declaration

All authors declare free of conflicts of interest for this research.

5.0 Sources of financing

The Department of Cognitive Neurosciences of Hospital Zambrano Hellion covered the expenses of the application and report of the ADOS-2 tests. The other expenses of this study were covered by the authors.

Tables and Figures

Table 1: Age, sex, and economic level on groups 1 and 2 and p values in positive cases for risk of asd**.**

Characteristics	Group 1	%	Group 2	%	p=*	p=
	n=25	50	n=25	50	Mchat+ Risk	Tod3+ Risk
Age in months 18-24 25-36 37-47	x=34.6 SD=8.8 5 14 6	 20 56 24	x=31.5 SD=8.4 5 9 11	 20 36 44	0.929	0.213
Sex Male Female	21 4	84 16	13 12	52 48	0.004	0.008
SEL AMAI** A/B (highest) C+ C D+ D E (lowest)	0 15 8 1 1 0	0 60 32 4 4 0	1 17 7 0 0 0	4 68 28 0 0 0	0.275	0.526

SD= standard deviation. *p significative value <0.05. ** Socioeconomic level, according to the Mexican Association of Intelligent Marketing and Opinion [11].

Table 2: Test Results Of Tests And Global Predictive Value Of Mchat-Es And Tod3**.**

	General Group	Gp.1 (Asd)	Gp. 2 (Healthy)	Falses	GPV*
Results	Positive/Negative	Positive/Negative	Positive/Negative	Positive/Negative	
Mchat-Es	29/21	25/0	4/21	3/1	92%
Tod3	25/23	25/0	0/25	0/2	96%
Ados-2	27/23	25/0	2/23		

*GPV= General Predictive Value.

Table 3: comparative results between mchat-es and tod3.

Test	Sensitivity	Specificity	PV+	PV-	LR+	LR-	PVT
Mchat-ES	96%	86%	89%	95%	0.04	0.040	92%
Tod3	92%	100%	100%	88%	∞	0.08	96%

PV=Predictive value. LR=Likelihood Ratio. PVT=Predictive value total.

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