

Autism Spectrum Disorder: What Study We Need to Do?

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Autism Spectrum Disorder (ASD) is a neurodevelopment disorder that must be present from birth or early childhood according to DSM-V.

The identification of ASD is of great importance for the early onset of the intervention and consequently, a more favorable prognosis.

The ASD according to the new definition, include autistic disorder (autism), Asperger disorder, childhood disintegrative disorder and pervasive developmental disturbance without further specification.

For a diagnosis of ASD, need to fulfill all criteria A, B, C, D – Table 1.

A - Clinically significant and persistent deficits in social communication and social interactions, not considering the overall developmental lag, manifested in all of the following ways:

1-Deficits in socio-emotional reciprocity; From abnormal social approach and conversation failure due to reduced sharing of interests, emotions and lack of social interaction initiative

2-Deficit of nonverbal communicative behaviors used in social interaction; From poor verbal and non-verbal communication, such as changes in eye contact and body language, deficits in the understanding and use of non-verbal communication, to total absence of facial expressions or gestures.

3-Deficits in developing and maintaining relationships at the developmental level (beyond those with caregivers); From difficulties in adjusting behavior in different social contexts, difficulties in sharing imaginative play and in making friends until the apparent absence of interest in people.

B -Restrictive and repetitive patterns of behavior, interests, and activities manifested by at least 2 of the following ways:

1-Speech, motor movements or use of objects in a stereotyped or repetitive way (simple motor stereotypes, echolalia, repetitive use of objects or idiosyncratic phrases)

2-Excessive adherence to ritualized routines and patterns of verbal and non-verbal behavior or excessive resistance to change (such as motor rituals, insistence on the same routes or foods, repetitive issues, or excessive stress at small changes)

3-Highly restricted and fixed interests that are abnormal in their intensity or focus, such as strong attachment or preoccupation with unusual objects, overly circumscribed interests persevering

4-Hyper or hypo reactivity to certain unusual stimuli or interests in sensory aspects of the environment (apparent indifference to pain / heat / cold, adverse response to certain sounds or textures, excessive smell or touch of objects, fascination with light or bright objects).

C -Symptoms must be present early in childhood (but may not manifest completely until social requirements exceed the limits of their abilities).

D-The symptomatology limits and disturbs the day to day functioning.

Table 1: Autism spectrum disorder – DSM-V criteria.

In the last 25 years, the numbers of cases of ASD increased from 0.5/1000 to 9/1000 under the age of 8 years. The prevalence is 4(M)/1(F). In 75 - 80% of cases, its etiology is unknown.

In some cases, patients with ASD also can have mental retardation, epilepsy, structural cerebral malformations, dysmorphism, microcephaly and macrocephaly.

Why is so important to find an etiology?

We can start a treatment (pharmacological and intervention strategies), to know what is the prognosis, do prevention and offer prenatal diagnosis and genetic counseling for the couple.

What are the exams that we need to do in a patient with criteria of ASD?

Mainly, cytogenetic examinations, metabolic study, neuroimaging and electroencephalogram(EEG):

Cytogenetics examinations

1. Chromosomal Microarrays Analysis (aCGH) is the first-choice test for cases of ASD with moderate to severe cognitive deficit of unknown etiology. Can diagnose about 10% of cases.
2. Molecular study for X-fragile syndrome
It is due to the mutation of the FMR1 (Fragile X Mental Retardation 1) gene at the Xq27.3 level, with repeat of the CGG triplet. Is considered
Normal-5-45 repetitions, Intermediate-46-54 repetitions
Pre-mutation- 55-200 repetitions, Mutation > 200 repetitions
Detected in 1 to 3% of children with ASD.
About 50% of patients with X-fragile syndrome present ASD behaviors and 71% of children with FMR1 pre-mutations have criteria for ASD. Currently this test is indicated in all cases of ASD.
3. PTEN macrocephaly syndrome: PTEN gene mutations were associated with autism and progressive severe to extreme macrocephaly (head circumference $\geq +3DP$). At birth, the head circumference is normal but subsequently increases exponentially in the first years of life. The child is macrosomic. This PTEN gene test is indicated in all cases of ASD with extreme macrocephaly ($\geq 3DP$).
4. Mutations of the MECP2 gene
Is located on chromosome Xq28 and is responsible for 96% of cases of Rett Syndrome.
Typical is a female gender with significant regression, epilepsy, microcephaly, inability to use pragmatic hands and stereotypies movements.
In 0.8 to 1.3% of ASD girls, we can find this gene.
In all cases of female with ASD and cognitive deficit, are indicated to study MECP2 gene.
5. Other studies

Depends on suggestive family history, presence of typical dysmorphic features and desired prenatal genetic counseling.

- a) Angelman / Prader-Willi Syndrome: Cytogenetic analysis by FISH or Chromosomal Microarrays of chromosome 15.
- b) Williams syndrome: Microdeletions of 25 to 30 genes in the q11.23 region of chromosome 7.
- c) Mutations of Genes 3/4 neuroligin (NLG3 and NLG4 - X chromosome): < 1% of ASD cases with patients showing motor tics.
- d) Gene Mutation Neuroxin 1: Are responsible for non-specific phenotypes.
- e) Gene SHANK3: Occur in 1.1% of patients with ASD. Is recommended in patients with severe speech and language deficits.
- f) Mutation of the HOXA1 gene. Search in patients with consanguinity, and ASD associated with deafness, truncus-encephalic anomalies and alterations in horizontal eye movements.

Metabolic studies

Inborn error of metabolism are rare causes of ASD. The diagnosis and the possibility of specific therapies can significantly change the prognosis.

1. Mitochondrial disease is associated with around 5% of cases of ASD.
2. Creatine deficiency: 80% of patients showed ASD, cognitive deficit and / or epilepsy.
3. Others metabolic screening depends on clinical presentation- Table 2
4. The metabolic test are:

Unexplained recurrent disease	Eye abnormalities (decreased visual acuity, cataracts, ophthalmoplegia, retinal abnormalities, opacity of the cornea)
Early Convulsions	Bone anomalies (disostoses, occipital prominences, calcifications)
Cyclic vomiting	Cutaneous anomalies (angiokeratoma, orange peel skin, ichthyosis)
Recurrent drowsiness / lethargy / coma	Hepatosplenomegaly
Ataxia	Arachnodactyly
Loss of psychomotor skills	Abnormal sexual differentiation
Hypotonia	Lactic / metabolic acidosis
Reduce growth velocity	Hyperuricemia
Unusual odors	Hyperammonemia
Unexplained deafness	Low Cholesterol
Dysmorphia or coarse face	Hypoglycemia

Table 2: Clinical findings and laboratory abnormalities suggestive of metabolic disease.

First line screening

- Blood count
- Glucose
- Liver function (ALT/AST)
- Renal function
- CK, uric acid, cholesterol
- Gasimetry
- Lactate and pyruvate
- Ammonia
- Plasma Amino Acids
- Organic acids
- Acylcarnitine on Guthrie Card

Second line screening

- Creatine Metabolism
- GAGs and oligosaccharides in urine
- Purine and pyrimidines in urine
- Thyroid function (TSH, freeT4)
- Biotinidase activity
- Homocysteine

Cerebral magnetic resonance with spectroscopy

Is only indicated in these situations:

- a) History and physical examination or neurological examination suggestive of CNS injury

- b) Microcephaly
- c) Extreme Macrocephaly
- d) Tuberous sclerosis
- e) Joubert syndrome
- f) Early environmental aggression
- g) Suspected mitochondrial disease or creatine metabolism deficit
- h) Signs suggestive of epilepsy or specific epileptic syndromes
- i) Regression of language after 4 years of age.

All ASD children need to do:

- a) Ophthalmology Evaluation: visual acuity, fundoscopy and check extra-ocular movements.
- b) Hearing Assessment: audiometry or auditory evoked potentials.

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