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Revision

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Autism spectrum disorder review: diagnosis and treatment update

Revisión del trastorno del espectro autista: Actualización del diagnóstico y tratamiento

Abstract

Autism spectrum disorder (ASD) is considered a multifactorial etiology during child's neurodevelopmental process covering the following clinical groups including: a) autistic disorder b) Rett´s Syndrome c) childhood disintegrative and d) widespread development. Affects 1 to 2/1000 people and is characterized by impaired in: a) social behavior b) deficit verbal and nonverbal c) restricted interests and repetitive behaviors, and d) changes in the scope of activities. The TEA persists lifelong and shows heterogeneity, ranging from mild personality changes to severe disability. The importance of this review is to provide a timely diagnosis in order to obtain a more favorable prognosis for the patient. The sections to treat are the symptoms, diagnosis and treatment. The relevance of this review is to provide and update information about ASD, so that it could guide the reader to fully understand the characteristics of this disease and the advances that have been developed to take appropriate treatment and improve the quality of patient's life.

Keywords

ASD, Autism spectrum disorder, Review, Diagnosis, Treatment.

Resumen

El Trastorno del Espectro Autista (TEA) es considerado una etiología multifactorial del neurodesarrollo infantil que abarca los siguientes grupos clínicos entre ellos: a) el trastorno autista b) los trastornos de Rett c) desintegrativo infantil y d) generalizado del desarrollo. Afecta entre 1 a 2/1000 personas y se caracteriza por alteración en: a) comportamiento social b) déficit verbal y no verbal c) intereses restrictivos y conductas repetitivas, así como d) alteraciones en el margen de actividades.

El TEA persiste toda la vida y muestra una gran heterogeneidad, que varía desde modificaciones leves de la personalidad hasta discapacidad grave. La importancia de la siguiente revisión es procurar un diagnóstico oportuno con el fin de obtener un pronóstico más favorable para el paciente. Las secciones a tratar serán la sintomatología, diagnóstico y tratamiento.

La relevancia del presente artículo radica en proporcionar al lector información ampliada y actualizada sobre el TEA, de manera que sirva como una herramienta para que el lector comprenda en su totalidad las características de esta patología y los avances que se han desarrollado para poder llevar un tratamiento adecuado y mejorar la calidad de vida del paciente.

Palabras clave

TEA, Trastornos del espectro autista, Revisión, Diagnóstico, Tratamiento.

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Introduction

Autistic spectrum disorder (ASD) affects one in every 700 to 1000 people; one in every 1000 presents classic autism symptomatology, generally affecting three to four boys per each girl at a global level. Autism disorder is a neurodevelopmental disorder under whose autism spectrum disorder umbrella encompasses five clinical groups including Rett syndrome, Asperger syndrome, childhood disintegrative disorder, and pervasive developmental disorder; it affects cognitive, emotional, and social skills and competency. The specific etiologies and neural bases of autism remain largely unknown; it has been proposed that alterations in multiple genes in combination with environmental factors constitute the cause for the development of the autism phenotype.[1,2,3]

Its manifestations are mainly cognitive and behavioral of variable severity, characterized by early dysfunction in communication and social interactions, presenting with repetitive, restrictive, stereotyped patterns of behavior and loss of interest in diverse activities. Additionally, it is frequently accompanied by impairments in adaptive functioning, sensory processing disorder, aggression, or self-injury. It is generally diagnosed clinically with the presence of central symptoms based on the criteria established by the DSM-V. Treatment of ASD must be individualized and there has been growing interest in the role of various pharmacological treatments.[4,5,6,7]

The importance of early detection and diagnosis by primary care physicians is that they know the disease and, should there be clinical suspicion, to refer the patient to a specialist or be treated, aside from supporting the adaptation of the patient with ASD to their environment. The social impact of timely intervention of patients has a positive effect on their environment and community when receiving the necessary support; the prognosis is very variable. It has been observed that patients with autism and their families have a lower quality of life directly related to higher traits of autism and deficits of executive functions.[8,9,10]

Definition

Autism spectrum disorder occurs in the early years of life. It is considered a multifactorial origin etiology, where genetics play an important role. Included in the category of ASD, based on the update of the DSM-V, are all generalized developmental disorders under the same diagnosis. These include autism disorder or Kanner syndrome, Rett syndrome, childhood disintegrative disorder, Asperger syndrome, and pervasive developmental disorder not otherwise specified / atypical autism.[8,9,11]

The ASD comprise a heterogeneous group of clinical expressions, whose main cause is unknown. Autism's clinical manifestations include social interaction and communication deficiencies with persistent deterioration, restricted and repetitive patterns of behavior, as well as deficiencies in social-emotional reciprocity, deficits in nonverbal communicative behaviors, and in the ability to develop, maintain, and understand relationships. Intellectual disability is frequent, with or without affecting of the cognitive competence and skills. It should be noted that the manifestations of ASD vary according to the severity of the autistic condition, level of development, and chronological age.[12,13,2]

Classification

Based on the classification of ICD.10 and the new update of the DSM-V regarding the types of autism (see Table 1), the ASD encompasses all generalized developmental disorders under a single diagnosis (except for Asperger disorder, which has been excluded from ASD in the DSM-V) that varies in age of onset, as well as in clinical presentation considering variations in cognitive, linguistic, behavioral and social skills.[13] (See Table 2)

The heterogeneity of the autistic disorder is due to different etiologies or combination of factors believed, according to the DSM-V, to be associated with known medical or genetic conditions, environmental factors, or other neurodevelopmental, mental or behavioral disorders. Primary autism is considered to be likely caused by an indeterminate genetic factor, and

Table 1. ASD Classification (Difference between DSM-IV and DSM-V)[13]

DSM-IV-TR Disorders of early childhood and adolescence	DSM-V Neurodevelopmental Disorders
Mental retardation	
	Intellectual disabilities
Generalized Developmental Disorders	Intellectual disability
Autism Disorder	Global development delay
Rett Syndrome	Intellectual disability not specified
Childhood Disintegrative Disorder	
Asperger Syndrome	**Autism spectrum disorder**
Pervasive Developmental Disorder Not Otherwise Specified	Autism spectrum disorder

Table 2. Classification and characteristics of generalized developmental disorders included in ASD[1]

Classification	Characteristics
Rett syndrome	It mainly affects pediatric female patients. Motor development is normal in the first six months. Later, there is a progressive loss of cognitive and motor skills, loss of positive pressure, language, social interaction, and interest in the environment. Stereotypies that characterize the syndrome appear later.
Childhood disintegrative disorder	Development is normal until two years of age. Before turning ten there is a loss of previously acquired language, social, interactive, and motor skills.
Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS)	Patients who do not meet all the manifestations of the autism disorder. (See Table 2)
Autism Disorder	Meet all criteria for autism disorder. (See Table 3)

secondary autism associated with known genetic alterations.[13]

Prevalence

It has been observed that the male-to-female ratio of incidence of this disorder is of 4:1, regardless of social or cultural classes. In Spain, during the seventies, autism was considered a disorder of low prevalence; however, it has since increased to 60/10,000 inhabitants suffering from ASD. American sources mention this number has increased from 1/1000 in 1998 to a 2002 accepted prevalence of 1/150-1/200 patient with ASD.[14,15]

Clinical manifestations

The clinical manifestations of patients with ASD are divided into three areas: a) deterioration in social interactions, b) verbal and nonverbal communication, and c) behavioral patterns and restricted and repetitive interests.[16] (See Table 3)

The clinical manifestations of autism are usually present between the year and a half and two years of age that remain stable during the preschool and school years. Typically, the average interval from the time parents begin to worry until they ask for help can be more than a year. During the first year the most consistent behavior in children with autism is: not responding to their name and not looking at faces or doing so rarely. During the second year, there is absence of interest in sharing experiences and inability to pay attention. The following are considered precocious signs: a) frequent tantrums and low tolerance to change; b) absence of babbling at nine months old; c) no signaling or gesticulation at one year of age, unresponsive when called by name; d) won't utter single words at sixteen months of age; e) absence of symbolic play at a year and a half; f) absence of two-word phrases at two years old. Any of the aforementioned findings should motivate a thorough investigation, considering

Table 3. Manifestations of autism.[16]

Manifestations	Characteristics
Deterioration in social interactions	• Patients may or may not show affection when interacting socially. • Older pediatric patients often do not point things out, instead, use eye contact. • They present lack of social interest, with an absence of friends, according to their age, or prefer to play alone.
Deterioration in communication	• In early childhood, some children do not babble and cannot compensate for this language deficit with facial expressions or gestures. • Immediate or delayed echolalia. • Concern about specific parts of toys.
Deterioration in patterns of behavior, and restricted and repetitive interests	• Behavior is restricted, repetitive, with stereotyped interests (child does not change toys or objects). • They can demonstrate atypical and impulsive behavior such as with objects, through unusual gestures, or with self-harming actions. • They repeat the same question several times, regardless of having received an answer, or participate in repetitive games. • They are concerned about their family, school environment, or routines.

autism one of the possible diagnoses. In a third of cases, the development is normal between the first and second year, and may later experience a gradual or unexpected regression, backtracking on previous development. Symptoms may also not be apparent to parents or teachers until four or six years of age.[17]

Patients may have cognitive abilities with moderate, severe, or profound mental retardation in IQ tests. With normal intellectual ability, the cognitive and language skills are often preserved; characteristically, they tend to misunderstand nonverbal messages, show difficulty in interpersonal relationships, especially when in a group, and possess few manipulative skills, are expressionless, speak with an abnormal tone, and focus on repetitive conversation topics that are interesting only to them.[17]

Diagnosis

Autistic spectrum disorder can be reliably diagnosed in children from the age of two years, with early intervention being beneficial for these patients. However, the average age for diagnosis is between three and six years. It has been postulated that one of the causes of this delay has to do with the great difficulty inherent in diagnosing these disorders at very early ages. Several factors contribute to this: a) symptom presentation is very variable and changes with age, b) social deficits and language delays may not be identified until the child begins to relate to peers in preschool.[6,16]

It is evident that the early detection of this disorder is crucial to aid the prognosis, the child's subsequent development, and the family's ability to adequately handle the difficulties that arise from this situation. We currently consider that around the year of life, and even earlier, the red flags for this disorder can already be identified. These signs are: little or no interest in visual contact, absence of orientation response when the child is named, absence of pointing, and absence of showing objects. This is fundamental because the earlier the diagnosis is made, the faster the child and his family can be given adequate help in order to promote an increase of achievements in functional abilities, communication, and intellectual processes.[2,18]

In early care, the diagnostic process of ASD should be based on the child's evolutionary history information, for which interviews will be conducted with parents, educators, and significant people in the child's life. Information will be collected regarding the child's neurobiological development, communicative, social, and motor developmental milestones, and on the appearance of the first autistic symptoms, as well as on their environment, their relationship style, behavior patterns, interactions with adults and children of the same age, level of participation in structured group dynamics, and their adaptation in the nursery or pre-school.[18]

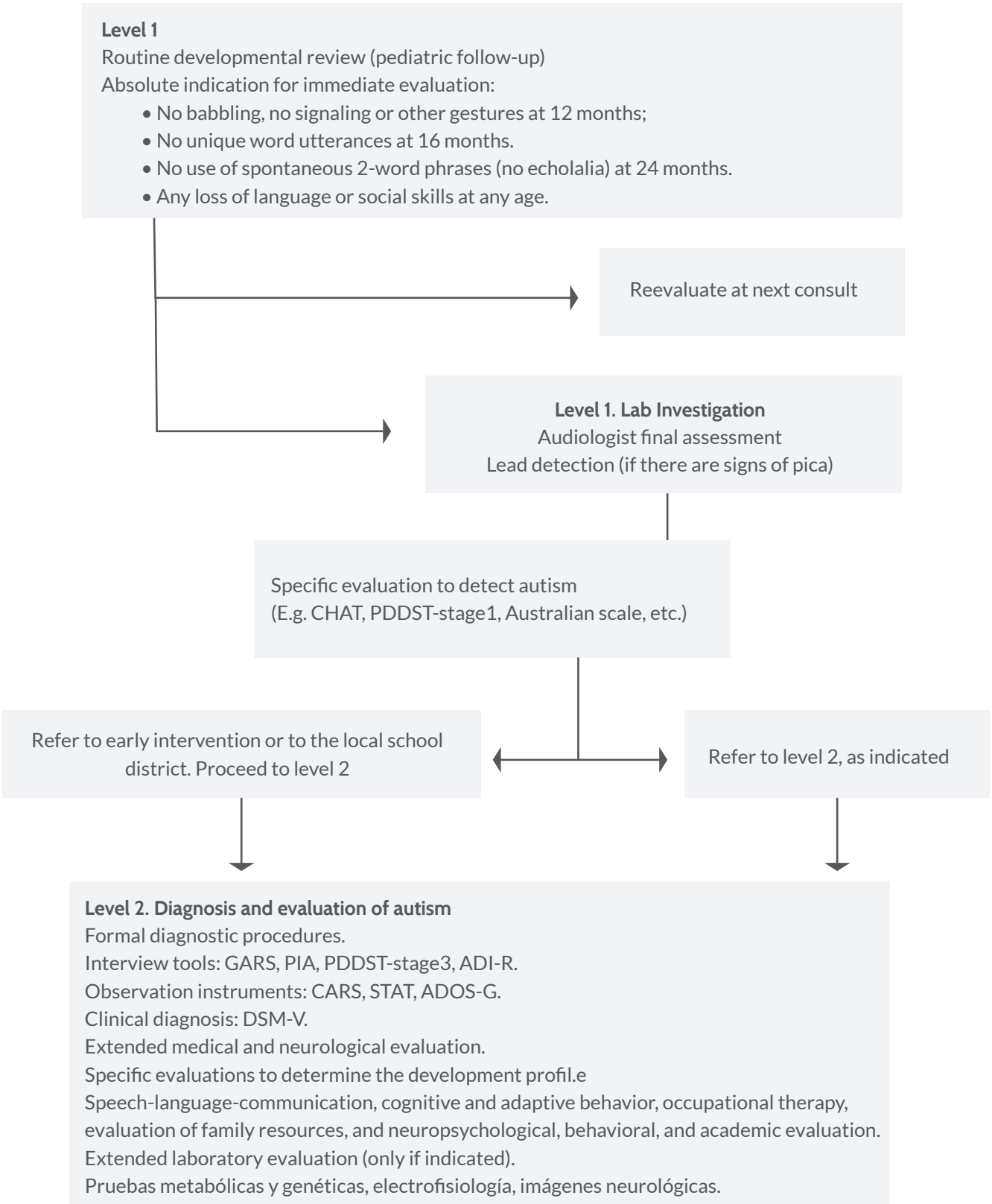
The American Academy of Neurology (AAN) in their report on identification and diagnosis of ASD, emphasize that a double approach is required. (See Algorithm 1) The first level deals with the strict monitoring of the neurodevelopment of children to discover any change or deviation from normal, for which it is desirable that doctors remain alert from the birth of the child. The second level in the diagnosis is to define the clinical characteristics of the child and then carry out three phases of evaluation.[19]

Phase 1, Identification of possible cases: the objective is to recognize the manifestations or to verify the observations of the parents regarding their child's communication, behavior, and social interaction.[19]

Phase 2, Global evaluation: seeks to observe the consistency and the significance of the child's neurological and behavioral manifestations, and to confirm the observations and concerns of the parents or physicians who referred the child to the specialist.[19]

Phase 3, Specific diagnosis: establishes the definitive diagnosis of ASD and defines its type. For this purpose the information provided by the parents and the specialists who have seen the patient is contrasted, applying the necessary tests

Algorithm 1. Diagnostic Levels for Autism.[1]



to correlate the data with the criteria of the DSM-V diagnostic manual.[19]

Caution is advised in the diagnosis of ASD due to nonspecific manifestations in different age groups. Early non-specific signs in infancy or small children include irritability, passivity, and difficulty sleeping and eating.[16]

Since autism does not have a diagnostic biological marker the judgment is strictly clinical, based on the behavioral manifestations given by the criteria of the DSM-V (see Table 4). The DSM-V manual mentions that the main features of autistic spectrum disorder are the persistent deterioration of social and reciprocal communication and social interaction (criteria A), and the behavioral patterns, interests, or restrictive and repetitive activities (criteria B). These symptoms are present since early childhood and limit or impede daily functioning (criteria C and D). The stage in which functional deterioration is obvious will vary according to the characteristics of the individual and his/her environment. The manifestations of the disorder also vary greatly depending on the severity of the autistic condition, the level of development, and the chronological age.[13, 20]

There is a wide variety of instruments for the diagnosis of autism spectrum disorder. The three most prominent are: a) The Modified Checklist for Autism in Toddlers (M-CHAT) is best applied in pediatric primary care during the recognition of the healthy child at a year and a half of age, the moment at which the symptoms become measurable and remain stable until preschool age between 16 and 30 months. It is a questionnaire addressed entirely to the parents consisting of 23 questions (see Table 5). b) The Autism Observation Scale for Infants (AOSI) studies children who have an older sibling with autism. c) The Childhood Autism Spectrum Test (CAST), for children between four and six years of age, is also a diagnostic tool.[17]

For definitive diagnostic confirmation there is a broad consensus on the use of validated tools such as The Autism Diagnostic Interview-Revised (ADI-R) and The Autism Diagnostic Observation Schedule (ADOS).[17]

Complementary tests

Laboratory. Laboratory tests almost never provide data for diagnosis, but in many cases are performed to rule out the symptomatic forms of autism, especially if there is an associated history of lethargy, cyclic vomiting, early epileptic seizures, dysmorphic features, and mental retardation.[1]

Neurophysiology. The electroencephalogram (EEG) tends to be normal in autistic children who do not have convulsions or clinical evidence of concomitant cerebral pathology.[17]

Neuroimaging. In idiopathic forms of autism, neuroimaging is usually normal; in some cases it observes hypoplasia of the posterior vermis and cerebellar hemispheres, reduction of the volume of the cerebral parietal lobes, and thinning of the corpus callosum.[1]

Genetic testing is not a routine study method for autism, and neither is metabolic screening, because less than 5% of patients will have an underlying metabolic disorder.[8]

Differential diagnosis

When a patient has some of the symptoms, a differential diagnosis should be made to rule out pathologies that may present similar symptoms, such as sensory anomalies, genetic or physical illnesses, since certain disorders or diseases may be accompanied by symptoms of autism and may require specific treatments. Among the most common are mental retardation / developmental delay, language developmental disorders, learning disabilities, hearing disorders, Landau-Kleffner syndrome, anxiety, and obsessive-compulsive disorder.[16]

Treatment

The objectives to keep in mind, in order to correctly treat children with autism spectrum disorder, should include: the patient's functional independence and quality of life, seeking to reduce the negative consequences of the disorder itself, facilitate development and learning of the individual, promote socialization, reduce disruptive

Table 4. DSM-V Diagnostic criteria.[13]

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested in the following symptoms, whether current or past (examples are illustrative, not exhaustive): 1. Deficiencies in social-emotional reciprocity vary, for example, from an abnormal social approach and failure of normal conversation in both directions, to a decrease in shared interests, emotions, or affections, to failure to initiate or respond to social interactions. 2. Deficiencies in nonverbal communicative behavior used in social interaction vary, for example, from poorly integrated verbal and non-verbal communication, to anomalies of visual contact and body language, or deficiencies in the understanding and use of gestures, to a total lack of facial expression and non-verbal communication. 3. Deficiencies in the development, maintenance, and understanding of a relationship range from, for instance, difficulties adjusting behavior in various social contexts, to difficulties sharing imaginative games, the ability to make friends, or even a lack of interest in other people. Specify current severity: Magnitude is based on impairments of social communication and repetitive and restricted behaviors.
B. Repetitive and restricted patterns of behaviors, activities, and interests, manifested in at least two of the following symptoms, whether current or past (examples are illustrative, not exhaustive): 1. Motor movements, stereotyped or repetitive use of objects or speech (e.g., simple stereotyped motor movements, aligning objects, spinning objects, echolalia, idiosyncratic phrases). 2. Insistence on sameness, inflexible adherence to routines or patterns of verbal and non-verbal ritualized behavior (e.g., extreme discomfort in the face of small changes, difficulties with transitions, rigid thought patterns, greeting rituals, need to always follow the same path, or eat always the same thing). 3. Highly restricted, obsessive interests that are abnormal because of their intensity or focus (e.g., excessive attachment or preoccupation with unusual objects, overly circumscribed or persevering interests). 4. Sensory hyper or hypo-reactivity or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain or temperature, adverse response to sounds or specific textures, excessive smelling or touching of objects, fascination with lights or rotating objects). **Specify current severity:** Magnitude is based on social and communicative disturbances and on the presence of repetitive and restricted patterns of behavior.
C. Symptoms must be present in the early developmental period (although they may not fully manifest until the demands of the environment exceed the child's abilities, or can be dissimulated in later life through learned skills).
D. Symptoms cause clinically significant changes in social, occupational, or other important areas of current functioning.
E. These alterations are not best explained by the presence of an intellectual disability (intellectual development disorder) or a global developmental delay. Intellectual disability and autism spectrum disorder often co-occur; to make a diagnosis of comorbidity of autism spectrum disorder and intellectual disability, social communication must be below expectations as a function of the general level of development.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger syndrome, or pervasive developmental disorder not otherwise specified should be diagnosed with autism spectrum disorder. Individuals who have marked deficits in social communication but whose symptoms do not meet the criteria for autism spectrum disorder should be evaluated for social (pragmatic) communication disorder.
Specify if:
It is accompanied or not by intellectual disability.
It is accompanied or not by a language disorder.
It is associated with a medical or genetic condition or with a known environmental factor (coding note: use an additional code to identify the medical or genetic condition).
It is associated with another mental or behavioral neurodevelopmental disorder (coding note: use additional code(s) to identify the associated mental or behavioral neurodevelopmental disorder).
With catatonia (coding note: use additional code 293.89 [F06.1] catatonia associated with autism spectrum disorder to indicate the presence of concurrent catatonia).

behaviors, and educate relatives and teachers to have an active participation in these during the intervention.[21]

It is necessary, in order to carry out the treatment, the participation of a multidisciplinary team that includes specialists with knowledge of diagnosis and treatment of autistic spectrum disorders, relatives, teachers, and people who maintain direct contact with the child that generate some influence through interactions.[21]

Intervention-based practices include clinical-educational strategies based on research of relevant interest groups, which can be taken into consideration while planning appropriate treatment for the patient.[22] (See Table 6).

There are global models of treatment that have shown positive results when applied; however, each of these models differ in terms such as the age of onset in which to start the application, the influence of the environment, actions regarding the answers obtained, individualization of the child, and reinforcements to apply. It is necessary to evaluate all variables that influence the way the treatment will be handled to be able to choose an adequate model to apply in order to achieve an adequate interaction of the child with its environment, developing as well the language and socialization skills.[22]

Appropriate pharmacological treatment for children with autism spectrum disorder should take into consideration the general basic care that any pediatric patient receives, such as prevention and immunization campaigns. Recommendations directed to a specific pharmacological treatment are based only on case studies and literature, which can be taken into consideration during the selection of the appropriate drug in each case.[21]

The main symptoms to be treated in patients with autism spectrum disorder are: epilepsy, aggression, hyperactivity, irritability, attention deficit, poor social interaction, obsessions, and anxiety. Individual treatment should take into account factors such as: to start with monotherapy to avoid the occurrence of any adverse drug reaction; administer low doses and adjust them according to the effect it produces in the patient; follow-up; take into consideration the pharmacokinetic and pharmacodynamic factors of each drug.[23]

A pharmacological treatment administering oxytocin, a neuropeptide related to social attachment and the development of bonding via a single intranasal dose, was linked to facilitation in the processing and retention of social information and recognition of emotion in relation with language intonation; however, this type of therapy is still subject to investigation and hasn't produced sufficient data to verify its effectiveness and to consider it an adequate treatment.[24]

Table 5. M-CHAT. [6]

1. Does your child enjoy being rocked, bounced on your knees, etc.?
2. Is your child interested in other children? *
3. Does your child like to climb to places, such as to the top of the stairs?
4. Does your child enjoy playing peekaboo, hide-and-seek, or other similar games?
5. Does your child pretend to, for example, serve a cup of tea or simulate other things? *
6. Does your child use the index finger to signal, to ask for something?
7. Does your child use the index finger to point, to show interest in something? *
8. Does your child know how to play with small toys (such as cars or blocks) and not just put them in their mouth, touch them, or throw them away?
9. Has your child ever brought an object to show you something? *
10. Does your child look into your eyes for more than a second or two?
11. Has your child shown hypersensitivity to noise (for instance, covering the ears)?
12. Does your child laugh in response to your face or your smile?
13. Does your child imitate you (for example, when you make a face)?
14. Does your child answer to his/her name when called? *
15. If you point to a toy in the room, does your child look at it? *
16. Does your child walk?
17. Does your child make strange movements with the fingers close to his/her face?
18. Does your child look at the things you're looking at?
19. Does your child try to call attention towards his/her own activities?
20. Have you ever wondered if your child is deaf?
21. Does your child understand what people say?
22. Does your child sometimes stare ahead or wander aimlessly?
23. Does your child look at your face to check your reaction when finding something unfamiliar?

* These are the critical questions, the most indicative of the existence of autistic features.

Table 6. Intervention Practices.[22]

Preventive behavioral	Give different types of visual, physical and verbal stimuli to achieve the desired response.
Behavioral intervention	Look for alternatives to reduce behavioral problems.
Molding	Reinforce the desired behavior by imitating it.
Joint attention	Increase the response to the perceived behavior of other people.
Natural context	Teaching of daily activities.
Parental intervention	Family participation.
Peer learning	Interactions with other children.
Pivotal behaviors	Motivation, spontaneous initiation, response to multiple signals, and autonomy.
Strategies for autonomy	Favor the child's independence.
Work systems	Organize areas for play and other activities.
Visual support	Use visual cues to maintain a behavior or ability.

Another treatment of interest is secretin, which is a gastrointestinal polypeptide involved in digestion, and that in intravenous infusion therapies has been associated with an improvement in socialization, cognitive, and communication skills thanks to its intervention as a neurotransmitter; however, like other hormonal therapies, there isn't enough evidence to be able to demonstrate its true therapeutic value. On the other hand, melatonin is a neurotransmitter whose main therapeutic function is the induction of sleep in patients with insomnia problems. Specific effects of its application in autism have not been demonstrated, its use is based on simply treating sleep disorders in children with autism to produce a sedative effect, but its excessive use can cause adverse effects such as dizziness, lethargy, and headache.[25]

Among the main drugs used in the treatment of autism are typical antipsychotics such as haloperidol, thioridazine, chlorpromazine and the atypical risperidone, olanzapine and clozapine, whose use is more common. These are used with the objective to treat the child's behavioral problems by blocking the D2 dopaminergic channels, causing a diminished reaction to stimuli known as "neuroleptic syndrome," observed as calm and quiet behavior in the child. In turn, some atypical antipsychotics also exhibit an antagonism of type 2A receptors for serotonin, aside from their effect on the D2 channels. It is important to individualize the patient when these drugs are administered, since there are no pre-established criteria for dosing and could present extrapyramidal adverse effects such as tremors, sialorrhea, sedation, impaired liver function, etc. This therapy should be suspended if no changes are perceived in the patient's behavior within six weeks.[23,25]

Risperidone is now considered the safest and most effective antipsychotic in the short-term treatment of autism, although it has been linked to a significant increase in weight of about two kilograms when used in 12-week trials. The effects of haloperidol have also been shown to be as effective as those produced by risperidone. Caution should be exercised when using clozapine in treatment because of the high risk of granulocytosis as an adverse effect; olanzapine is useful to treat children and adults but with minor adverse effects such as increased appetite and weight gain. Even with limitations in its study, intramuscular application of paliperidone has shown improvements in suppressing irritability and aggression in patients with autism, and its only adverse effect is the increase in appetite. Treatment with aripiprazole can be extended up to one year due to its safety and good tolerance in children and adolescents with autism.[25,26]

Olanzapine also produces an improvement in the treatment of irritability and hyperactivity in autism with lesser effects than risperidone, but with more marked adverse effects such as weight gain, so its use is recommended more for the treatment of adolescents rather than of children.[25]

Attempts have been made to test the efficacy of a placebo treatment for autism in order to avoid some of the adverse effects of drugs such as haloperidol and risperidone; however, placebos have not shown any favorable outcome against any other type of pharmacological therapy.[25]

Serotonin reuptake inhibitors such as fluoxetine, paroxetine and sertraline are given to children with autism because they have been found to increase 25% of serotonin levels in platelets and serum. This treatment is based on suppressing symptoms such as anxiety, depression, obsessive-compulsive disorders, and self-injurious behavior.[23]

Clomipramine has shown favorable results in reducing symptoms such as repetitive behaviors in children with autism with effectiveness similar to haloperidol; however, the intensity of the effect varies with each patient and the doses have to be individualized to avoid adverse effects such as dry mouth, constipation, lethargy, depression, and sleep and behavior problems. Fluvoxamine is effective in treating repetitive and aggressive behavior, but the percentage of effectiveness in patients is very low and very poorly tolerated leading to anxiety, irritability, lack of concentration, and aggressive behavior, among other adverse effects.[27]

The effects of fluoxetine are more effective during adolescence than at any other age. Sertraline has been shown to be well tolerated and moderately effective in treating repetitive and aggressive behavior with a minimum amount of adverse effects such as weight gain and anxiety. The use of citalopram brings a wide range of adverse effects such as hyperactivity, impulsivity, insomnia, diarrhea, and dry skin, and is merely used to treat symptoms secondary to behavioral problems. Effective therapy in children for hyperactivity may require the use of multiple drugs such as venlafaxine with serotonin and noradrenaline receptor inhibitors. Mirtazapine is a tricyclic antidepressant which antagonizes serotonin receptors and α-2 adrenergic receptors, showing a very low incidence of adverse effects during its use to treat anxiety, irritability, and hyperactivity.[27]

A series of indistinguishable behaviors may be associated with variable epileptic seizures in children with autism. The administration of antiepileptic drugs such as sodium valproate, carbamazepine, lamotrigine and topiramate, among others have action mechanisms focusing on blocking sodium and calcium channels, reducing excitatory glutamatergic activity, and increasing inhibition by GABA. The administration of these drugs is directed towards the resolution of these crises without taking into consideration the presence of autism in children. Electroencephalogram studies may associate the presence of autism with the manifestations of seizures by finding temporary unilateral or bilateral paroxysms in the temporal lobes.[23,25]

Studies have investigated a possible increase in the permeability of the intestinal barrier, so specific diets have been considered for children with autism. Such diets involve the elimination of products such as gluten or casein, found in products such as wheat and milk, since their activity has been linked to opioid effects. The ketogenic diet includes a high fat content and a low amount of carbohydrates that leads to the formation of ketone bodies by the liver and these are linked to a lower incidence of epileptic seizures. The proposal to include supplements in this type of diets such as magnesium and vitamin B6 has also been evaluated, but there is no evidence that any specific diet plan has beneficial effects in children with autism.[25]

Prognosis

In general, patients' prognoses are variable, they depend on the early attention given and also on the severity of the underlying etiologies. The best prognoses belong to patients who have access to different treatments and with socio-familial conditions that favor their development. Some factors are associated with better prognoses: the development of some communicative language before the age of six, presence of slight or no mental retardation in nonverbal intelligence tests, and psychotherapeutic intervention as early and as intensive as possible. The cooperation between specialists such as neurologists, psychiatrists, neuroscientists, psychologists, speech therapists, occupational therapists, and educators is crucial to continue to promote understanding and allow a more adequate approach to patients.[28,8,29]

Quality of life

In studies evaluating IQ, early language development, daily executive functions, and their influence on quality of life, children with ASD were found to have a lower quality of life than children with normal development. This inferior quality of life is related to higher levels of autistic features and deficits of executive functions. It is recorded that, in addition to the patient, the family has a significant reduction in the quality of life affecting different domains (economic, social, educational, and psychological). It is recommended to work with the aggravating factors in autism and the deficits of executive functions that are more associated to an inferior quality of life. The intention is to improve the interventions and, together with the individualized treatments, to improve the quality of life in patients and their families and, in turn, become a useful tool for evaluating treatment outcomes.[10,30]

Conclusion

The present article analyzed the main tools available with the objective of providing information for the early diagnosis and intervention for patients with ASD. It is essential to recognize its main and early clinical manifestations in the first years of life, so that the physician is able to offer the optimal clinical-educational and pharmacological treatment to improve the patients' prognosis and quality of life.

Conflict of interest
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