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Autism Spectrum Disorder (ASD): Definition, Contexts, Neural Correlates and Clinical Strategies

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Abstract

Starting from the general concept of "autism spectrum disorders", as contained in the manual of psychiatric disorders DSM, version V, we proceeded to contextualize the definition distinguishing it from other pathological forms (eg Asperger, disintegrative disorder of childhood, Rett and the pervasive disorder not otherwise specified), as was previously listed in the DSM-IV version, orienting the subject examined with a whole series of focus on neurobiological and clinical profiles. It then concluded with further attention to the therapeutic context, from the psychotherapeutic approach to the pharmacological one, to manage the pathological consequences of the disorder, with particular attention to the most important and recent scientific discoveries, such as etiological theories of the pathological condition and the best treatments to prefer. It was concluded that recent research in the field of neuroscience has contributed significantly to the reconstruction of a pathology with outlines and an etiology that is still not well defined. Giving value to the neuropsicobiological bases of autism, giving value to the technical profiles related to the microscopic alterations in specific brain areas, contextualizing in a more defined way also to behavioral disorders related to autism spectrum disorders.

Keywords: Psychology; Neurobiology; Neuroscience; Child Neuropsychiatry; Autism; Autism Spectrum Disorder; Pervasive Developmental Disorders; Asperger Syndrome; Pervasive Disorder Not Otherwise Specified; Disintegrative Disorder; Rett Syndrome

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Definition and Clinical Context of Autism Spectrum Disorder

Autism spectrum disorder is a disorder with developmental onset and represents a condition that affects about 1% of the population, in all age groups, even if the data relating to the most recent research shows an increasing incidence, with particular attention to the westernized world [1]. The incidence varies from 5 to 50 people per 10,000, depending on the diagnostic criteria used, which have developed and improved over time [2,3]. It mainly affects male subjects with a rate of two to four times (and sometimes even six to eight times) higher than the female sex it occurs almost always within the first 3 years of life [4]. A recent epidemiological study highlights a correlation between the risk of autism and the age of parents [5,6]. From the analysis of data collected by the International Collaboration for Autism Registry Epidemiology (iCARE) on 5.7 million children in five countries shows that the greatest risk is recorded in adolescent mothers and fathers over fifty. The percentage of autism was in fact 66% higher in children born to fathers "over 50" compared to those born to fathers in their twenties and 18% higher in children with adolescent mothers than mothers in their twenties. DMS-V, *autism* has been framed according to a new diagnostic orientation (2013) which, in addition to replacing the expression "*Pervasive (or generalized) developmental disorders*" with the term "Autism spectrum disorders", also eliminates the presence of the different subtypes of the pathology or forms of autism, such as [7,8]:

Asperger's Syndrome

It is a pervasive developmental disorder, now considered a subtype of the "high functioning" autism spectrum disorder. Individuals with the syndrome present persistent impairment of social interactions, repetitive and stereotyped behavior patterns, activities and interests in some restricted cases. Unlike autism, there are no significant delays in language development or cognitive development. Some symptoms of this syndrome are related to other disorders, such as non-verbal learning disorder, social phobia, schizoid personality disorder, depression, anxiety and obsessive-compulsive disorder. The tendential lack of cognitive empathy of subjects with the syndrome (otherwise called "lack of theory of mind", not to be confused with affective empathy, relative to the subject's ability to feel emotions and perceive those of others, that in individuals characterized by the syndrome it is not significantly altered, and it is typical instead of different disorders such as the antisocial one), it causes a significant impact on aspects of community life [9]. The inability to react adequately to social interaction may appear as a sort of contempt or indifference to the feelings of others and can be wrongly interpreted as a form of insensitivity [10]. However, they can sometimes show an unusual egocentrism. In fact, they accuse difficulties in elementary social interactions, difficulties that can include the lack of friendship development or the lacking of gratifications or relational realizations (for example showing other objects of interest), an absence of social or emotional reciprocity ("games"), social as giving and taking) and alterations in non-verbal behavior in areas such as eye contact, facial expressions, posture and gestures. However, people with Asperger's syndrome do not show the same limitations as those with autism (for example, unlike the latter, they are able to approach socially with others, even if awkwardly). An individual with the syndrome is able to engage in one-sided conversation, a long-winded discourse on a favorite topic, while struggling to understand or recognize the feelings or reactions of the listener, such as the desire to change the theme of the conversation or the willingness to terminate the interaction [11]. This social unease has been called "active but strange". Individuals with Asperger syndrome show limited and repetitive interests and activities, sometimes abnormally intense or involving exaggerated concentration. Inflexible routines can follow, presenting frustration at the slightest variation, behaving in stereotyped and repetitive ways. Although individuals with Asperger syndrome acquire language skills without significant delay and their ability to dialogue is generally devoid of significant anomalies, the use of language is often atypical [12]. There is a certain verbosity, abrupt transitions at the level of arguments and expressed concepts, literal interpretations of the words of the interlocutors and misunderstanding of the nuances of the language, use of non-significant metaphors for the interlocutor (to which they are often of little or no understanding) , auditory attention deficit, unusually pedantic dialogue, formal or idiosyncratic discourse and anomalies in the volume, tone and intonation of the voice, in prosody and rhythm [13]. Ecolalia has also been observed in some individuals with the syndrome [14]. The pursuit of specific and restricted areas of interest is one of the most predominant features of the syndrome. The diagnosis is generally formulated between four and eleven years of age. Since 2013, the diagnosis of Asperger syndrome has been removed from the DSM as a separate but classified condition along with autism spectrum disorders.

Rett's Syndrome

It is a serious neurological disease, which affects female subjects in most cases. The disease is congenital. Serious delays in language acquisition and in acquiring motor coordination can be observed. Often the syndrome is associated with severe or very severe mental retardation. Loss of performance capabilities is generally persistent and progressive. After an initial phase of normal development, there is a developmental arrest and then a regression, or loss of acquired skills. A slowing of the development of the skull is observed (of normal size at birth) compared to the rest of the body between the first 5 and 48 months of life; a normal psychomotor development within the first 5 months of life, with subsequent loss of previously developed manual abilities and the appearance of stereotyped movements of the hands (twist them, beat them, move them, tighten them). We are also witnessing a progressive loss of interest in the social environment, which however in some cases reappears with adolescence. May also be present: irregularities in breathing; EEG anomalies; epilepsy (over 50% of affected people have had at least one epileptic seizure); increased muscle stiffness with age, which can also cause muscle deformity and atrophy; broad-based walking (in about 50% of subjects); scoliosis; growth retardation.

Disintegrative Disorder

It is Heller's syndrome or childhood dementia or disintegrative psychosis. It is a rare and extremely severe pervasive developmental disorder. It is also known as "regressive autism" and often causes the loss of physical or cognitive abilities previously acquired by the child as well as blocking progress. It affects about 17 in a million. The child affected by this syndrome encounters, after the first two years of life, but always before the age of 10, a significant loss of previously acquired skills in at least two of the following areas: language; social relations; sphincter control; motor skills. Childhood disintegrative disorder is often associated with severe mental retardation [15].

Pervasive Disorder not Otherwise Specified

This category was used when there was a serious and generalized impairment of the development of reciprocal social interaction associated with a compromise of verbal or non-verbal communication skills or with the presence of stereotyped behavior, interests or activities, but the criteria for a specific Pervasive Developmental Disorder, Schizophrenia, Schizotypal Personality Disorder or Personality Avoidance Disorder. For example, this category included "atypical autism" - frameworks that do not meet the criteria for Autistic Disorder for the late age of onset, atypical or subliminal symptoms, or for all these reasons together. Today, the category to which the disorder refers is that of neurodevelopmental disorders, but the areas of developmental impairment remain substantially the same as in the DSM-IV [16].

This new wording draws attention to the dimensional concept of autism, characterized by behaviors that extend seamlessly between normality and disease, but that differ because the frequency and intensity of that symptom do not allow it to adapt to the context, to develop cognitive resources, to acquire and maintain social relationships. The fact that the disorder is considered within a "spectrum" means that the frequency distribution of a given problematic behavior varies over time and in the intensity of its manifestation. This means that within the dimensions, or symptoms of autism, there are people with heterogeneous clinical features in social impairment and in the presence of repetitive behaviors and restricted interests. Individuals with spectrum disorders of autism would share the impairment of social and communication functions associated with restricted interests and stereotyped behaviors. However, the presence of intellectual disability (according to the latest research in 30% of subjects) and the presence of associated symptoms, including motor and attention instability, and other behavioral disorders, hypersensitivity to sounds and high pain threshold, contribute to broad clinical heterogeneity. For this reason, at present, given the variability of the spectrum, we prefer to speak of "autisms", in the plural.

In DSM-IV, *autistic disorder* (included in pervasive or generalized developmental disorders, together with Asperger, Rett, disintegrative disorder and generalized developmental disorder not otherwise specified) was diagnosed using these diagnostic criteria:

- A total of 6 (or more) entries from 1), 2), and 3), with at least 2 from 1), and one each from 2) and from 3): 1) qualitative impairment of social interaction, manifested with at least 2 of the following: a) marked impairment in the use of various non-verbal behaviors, such as the gaze direct, mimic expression, body postures and gestures that regulate social interaction; b) inability to develop relationships with peers appropriate to the level of development; c) use of stereotyped and repetitive language or eccentric language; d) lack of spontaneous research in sharing joys, interests or goals with other people (eg. not showing, bringing or calling

attention to objects of personal interest). 2) qualitative impairment of the communication as expressed by at least 1 of the following: a) delay or total lack of the development of the spoken language (not accompanied by an attempt to compensate through alternative methods of communication such as gestures or mimicry); b) in subjects with adequate language, marked impairment of the ability to initiate or sustain a conversation with others; c) lack of various and spontaneous simulation games, or games of social imitation adapted to the level of development. 3) modalities of behavior, narrow, repetitive and stereotyped interests and activities, as expressed by at least 1 of the following: a) absorbing dedication to one or more types of narrow and abnormal stereotyped interests or by intensity or by focus; b) entirely rigid submission to unnecessary habits or specific rituals; c) stereotyped and repetitive motor anisms (beating or twisting hands or the head, or complex movements of the whole body); d) persistent and excessive interest in parts of objects.

- Delays or abnormal functioning in at least one of the following areas, with onset before 3 years of age: a) social interaction; b) language used in communication; c) symbolic play or imagination.
- The anomaly is not better attributable to Rett's Disorder or Childhood Disintegrative Disorder.

In DSM-V, on the other hand, autistic disorder has an autonomous structure, absorbing almost all previous pathologies, becoming "*autism spectrum disorder*", diagnosed according to these criteria (A, B, C and D):

a) Persistent deficit in social communication and social interaction in different contexts, which cannot be explained by a generalized delay in development and manifested by all three of the following points: 1) deficit in socio-emotional reciprocity that goes from an abnormal and unsuccessful social approach in the normal conversation (question and answer) through a reduced sharing of interests, emotions, mental perception and reaction up to the total lack of initiative in social interaction; 2) deficits in non-verbal communication behaviors used for social interaction, from a poor integration of verbal and non-verbal communication, through abnormalities in eye contact and in body language, or deficits in understanding and using non-verbal communication, up to the total lack of facial expressiveness and gestures; 3) deficit in the creation and maintenance of relationships appropriate to the level of development (not including those with parents and caregivers); ranging from difficulty in adapting behavior to different social contexts through difficulties in sharing imaginative play and making friends to the apparent lack of interest in people.

b) Pattern of restricted, repetitive behaviors, interests or activities as expressed by at least 2 of the following points: 1) language, movements or use of stereotyped or repetitive objects, such as simple motor stereotypes, echolalia, repetitive use of objects, or idiosyncratic phrases; 2) excessive fidelity to the routine, verbal or non-verbal behavior reused or excessive reluctance to change: motor rituals, insistence on doing the same road or eating the same food, incessant questions or extreme stress following minor changes; 3) highly restricted and fixed interests, abnormal in intensity or arguments: strong attachment or interest in unusual objects, excessively persistent or detailed interests; 4) hyper / hyporeactivity to sensory stimuli or unusual interests towards sensory aspects of the environment: apparent indifference to heat / cold / pain, adverse response to specific sounds or consistencies, excessive sniffing or touching objects, attraction to lights or spinning objects.

c) Symptoms must be present in early childhood (but may not become completely manifest).

d) The set of symptoms must limit and compromise daily functioning. The 3 severity levels are: - 3 (requires very substantial support); - 2 (requires substantial support); - 1 (requires support).

To sum up, to simplify, the autistic spectrum according to DSM 5 is therefore mainly characterized by symptoms relating to the areas of communication and social interaction: a) difficulties in socio-emotional reciprocity: presence of an abnormal social approach and difficulty in sustaining and maintaining a conversation with the other; reduced sharing of interests and emotions; inability or difficulty in developing an interaction with peers appropriate to the level of development; b) deficit of non-verbal communicative behaviors used for social interaction: anomalies of visual contact (lack of direct gaze), facial expressions, body postures, and understanding or use of the gestures that regulate interaction with the other; c) difficulties in the development and maintenance of relationships appropriate to the level of development: difficulty in adapting behavior according to the various social contexts, difficulties in the development and sharing of a game of imagination, lack of interest in peers.

The individual with autism spectrum disorder may or may not have a speech disorder. Finally, the age of onset,

which generally occurs before the age of three, can vary in particular in conditions of high functioning: the symptoms in this case emerge when environmental demands begin to be excessive for the child's abilities (for example, at the entrance to the elementary school). In some cases, children who receive a diagnosis of autism spectrum may seem different from an early age. Parents are usually the first to notice unusual behavior in their child. People with autism, therefore, grow differently from the majority of other people, with respect to communication and social interaction; they also present peculiarities in the game and often show difficulty in sharing the meaning of symbolic play and making social games with other children. However, it is not unusual for all ages to find repetitive behaviors and routines, particular interests or sensorial peculiarities.

The Neural Correlates in Autism Spectrum Disorder

Neuropsychological research attempts to explain the complicated functioning of the "autistic" mind by studying the cognitive, social and emotional competences of individuals with autism, while other lines of research analyze the functioning of the brain in search of the possible neurobiological basis of the syndrome, adopting various investigation techniques such as neuro-image techniques, neuro-functional and neuro-transmitting investigations to bring behavioral symptoms back on a neurophysiological basis. In 2017 an extremely relevant study was conducted at Washington University, which made two important discoveries. The first refers to that particularity of the brain of children with autism spectrum disorder already mentioned, or the presence of an excess of synapses or connections between neural cells [17]. The second has to do with an experimental treatment that could regulate this hyperconnectivity, this unique brain alteration that occurs before the 3 years of life. However, the aspect thus treated would seem simplistic, since we cannot ignore that besides this synaptic singularity, there are also other associated problems, such as the alterations in communication between the different brain areas: one of the causes of autism could be caused by a lack of connectivity between the different areas of the brain, which originates when microglia fails in its role as a "brain sweeper" and fails to eliminate unnecessary neuronal connections at a crucial stage of the maturation of the nervous system [18].

On the basis of thousands of researches, therefore, up to now it is impossible to highlight morphological and biochemical alterations common to the various spectrum disorders; however, many pathogenetic theories are proposed that seem to be confirmed in some subgroups of subjects with an autism spectrum disorder: abnormal development of some brain structures and levels of connection between different areas, dysfunctions of neurotransmitters at the level of the central nervous system, immunological abnormalities , autoimmune processes, metabolic disorders.

At morphological / histological level, some autopsy studies conducted on brains of autistic subjects compared with normal subjects have shown that some brain structures, such as the cerebellum, entorhinal cortex, hippocampus and amygdala, show increased density of nerve cells and small size of the same [19,20]. Some recent studies conducted through neuroimaging techniques, seem to indicate abnormalities in the connections between neurons in specific brain areas such as the auditory cortex, and the mirror neuron system, as well as variations in the volume and symmetry of the two cerebral hemispheres [21-26]. These evidences suggest that very early defects (first trimester of pregnancy) in the organization of the brain are partly responsible for the behavioral and neurological alterations of the autistic syndromes. At the cellular level the most investigated hypotheses concern the anomalies in the functioning of the synapses, especially the inhibitory ones, mainly mediated by γ-aminobutyric acid (GABA), as well as defects in the synthesis and release of serotonin (5HT), a neurotransmitter involved in modulation of social behavior. Many studies also show alterations in the mechanisms involved in the changes that take place inside the brain cells in response to nervous stimulation, mechanisms linked to intracellular calcium [27].

Finally, systemic abnormalities have also been reported that could help explain the complex etiopathogenesis of autism. Autopsy studies and also the analysis of cerebrospinal fluid in patients have shown alterations of the immune system and increase of various molecules involved in the processes of inflammation at the level of the central nervous system [28]. Recently theories have been suggested concerning the presence of maternal antibodies that would cross the placental barrier contributing to the immune and neurological abnormalities observed in autistic children [29]. The link between oxidative stress and autism is actively studied [30]. In some autistic subgroups an altered metabolism of steroids and in particular testosterone and cholesterol has been found [31,32].

The high prevalence of autistic disorders in males has suggested that the genetic vulnerability characteristic of autism may be susceptible to the hormonal environment (neuroendocrine factors) that characterizes embryonic and fetal development. In males, development is dominated by the presence of androgenic hormones, such as testosterone, compared to that of females where estrogens prevail. These considerations are the basis of the theory that sees the brain in autism as an "extreme male brain" [33,34]. A recent study carried out on autopsy brains of young adults diagnosed with autism, identified a new candidate gene in the etiopathogenesis of autism involved in processes of brain differentiation during development. The translation of this gene depends on the action of hormonal factors such as androgens and estrogens [35].

Oxytocin - a hormone considered an important regulator of social behavior in mammals including humans "appears in several studies as a hormonal factor involved in the behavioral symptoms of the autistic spectrum. Clinical studies have shown that treatment with oxytocin may modify some behavioral aspects (for example the recognition of facial expressions, and the ability to participate in a game that involves interaction with others) in children with high-functioning autism [36,37]. Many studies have tried to associate the presence of autistic disorders with genetic alterations involving the oxytocin gene and / or its receptor These studies suggest that the function of oxytocin could be modulated in autism by mutations of the oxytocin receptor gene, but also by 'epigenetic' modifications, ie from non-congenital modifications that although not changing the nucleotide sequence, determine undermine an alteration in the expression of that gene [38].

Furthermore, a new study recently published links for the first time the lack of development of a specific area of the brain to disorders of the autistic syndrome [39]. The research focused on the coordinated action of two molecules, Negr1 and FGFR2, which ensure the correct development of the somatosensory cortex, a specific brain area dedicated to the perception and processing of sensory stimuli. The researchers found that an alteration of the function of Negr1 and FGFR2 induces defects in the formation of the cerebral cortex and leads to abnormal behaviors that can be traced to the diagnostic symptoms of autism. In particular, the researchers reconstructed the mechanism by which the Negr1 and FGFR2 genes cooperate in regulating the earliest stages of brain development, influencing the migration of neurons within the fetal brain and controlling their correct positioning; the researchers turned off their expression in specific neuronal populations and observed important effects on the migration and morphological development of those cells: the absence of Negr1 or FGFR2 hinders the path of neurons towards the upper cortical layers and reduces the development of neurites. The mutations of the Negr1 and FGFR2 genes had in fact been observed in individuals suffering from autism spectrum disorders, but it was not known whether the two genes were somehow related and how they cooperated in regulating brain development.

Causes, Diagnosis and Treatments

To date it is increasingly important to identify the symptoms of autism at an early stage, so as to act on the processes of development undergoing training. Current research supports the importance of early diagnosis (around 18 months) in order to obtain better results in the intervention [40]. Several studies report that interventions beginning before 4 years of age are associated with improvements in the cognitive area, language, adaptive behavior, daily life skills and social communication. However, currently the diagnosis of autism is still relatively late (around 3-4 years). The diagnosis can be made, at the present time, only based on the presence of behavioral symptoms, which have been defined by the World Health Organization, at any age, if the symptoms have been present since childhood, and, in cases with a better functioning can also be placed in adulthood.

In making the diagnosis of autism, it is important to carry out a complete evaluation, which provides an exhaustive picture of the child's condition. The assessments that must be made in this regard are: a) diagnostic evaluation: through the tools of ADOS-2 or CARS2 / CARS2-HF, it is possible to evaluate the presence or not of the symptoms necessary to affix the diagnosis; b) functional evaluation: it allows to know the strengths and difficulties of the child and to calibrate the intervention on its specific needs; c) normative evaluation: it aims to analyze the intellectual level of the child (IQ), based on the comparison with the average values of the peer group. Furthermore, given the high variability of the characteristics of autism and the similarity of some of these with other morbid conditions (eg developmental delay, language delay, dyspraxia, hyperactivity, depression, etc.) it is necessary that the diagnosis be made by a team of people with specific training and experience (psychologists, neuropsychiatrists, speech therapists, neuropsychomotors, tenured teachers and education assistants). Compared to the causes, again, they

are the subject of constant investigation. It is now believed that a single cause cannot be identified for all the different forms of autism. There is strong evidence that autisms can be caused by a variety of physical factors, which influence brain development. The brain activity of autistic people, observed with image techniques (functional magnetic resonance) and other investigation techniques, results in fact different from that of the control subjects, for example a lower neural connectivity was found at interhemispheric level at middle and long range. There is also a relationship between autism and epilepsy, although many people with autism never show the characteristic changes in epilepsy in life. It is now clear that the cause is not emotional deprivation or the way a person has been raised, although educational aspects can then affect behavior. Recent studies confirm the role of a genetic predisposition: in particular, rather than a single gene, multiple genes would seem to explain the vulnerability to the disorder. It is likely that more genes are responsible for autism, rather than a single gene, which interact with each other and with environmental factors. It is no coincidence that in a recent research the direct correlation between autism and genetic mutations of the parents of the unborn child has been shown: some of the mutations related to autism spectrum disorders are inherited from the genetic material of germ cells and affect mostly spermatozoa [41]. Particular mutations that accumulate in specific areas of DNA derive instead from the egg cell. To date, there are no genetic tests able to diagnose the predisposition to an autism spectrum disorder, nor are there other organic markers able to allow a diagnosis of autism. At present, the diagnosis can be made or excluded only based on the presence or absence of behavioral symptoms. A further study, to be confirmed by other research, has stated that the rapid development of the cortical surface and the volume of the brain in the first and second year of life seems to be related to a high risk of developing an autism spectrum disorder [42].

Given the high individual variability, there is no single specific intervention that is valid for everyone in the same way [43]. Furthermore, it is rarely possible to achieve total remission of symptoms. For this reason, there are many different treatments for autism. The "Autism Intervention Guidelines" published by the National Research Council [44] state: a) there is no single intervention that is good for all autistic children; b) there is no single intervention that is suitable for all ages; c) there is no single intervention that can respond to all the multiple needs directly or indirectly linked to autism.

On the other hand, the continuity and quality of the therapeutic path are guaranteed through: a) the involvement of parents throughout the journey; b) the ongoing choice of intermediate objectives to be achieved and therefore of the interventions to be activated (diachronic perspective); c) the coordination, at every stage of development, of the various interventions identified for achieving the objectives (synchronic perspective); d) verification of the strategies implemented within each intervention.

An early and intensive intervention is recommended, which takes into account the need to intervene on the disorder of intentionality of the child. It is therefore important to work early not in the sense of behavioral training, but rather in the development of autonomous motor and communication intentionality. People with an important communication disorder, as in DSA, in disorders with severe receptive difficulties and also in verbal dyspraxia, can also benefit, as Rapin suggests, from cognitive supports such as communication tables, sign language, learning of language using the computer, of reading illustrated educational materials and other communicative tools. These supports must be provided early, in order to: increase the level of language learning; make the most of the time needed to learn the child's language; minimize secondary behavioral consequences to inadequate communication skills; to anticipate the subsequent potential difficulties with the acquisition of written language. The targeted use of drugs is aimed at the reduction or extinction of some problematic behaviors, or associated clinical disorders such as epilepsy and attention deficit, in order to avoid further clinical aggravation or to improve the quality of life.

In many countries, psychologists and psychotherapists are involved in clinical intervention in autism situations, as well as other types of developmental disorders: not so much in the sense of the old type of psychoanalytic intervention directed only to the child, but also and above all in the forms of psychoeducational support for the child, of helping the family to support it and reducing possible dysfunctional aspects, in the clinical evaluation of the disorder and its functional correlates, as well as in collaborative work with educators, rehabilitators and teachers to usefully support children and families in cognitive and communicative rehabilitation, in psycho-pedagogical support, in clinical intervention on behavioral problems, and in supporting psycho-affective development processes, integrating a series of multidimensional interventions in what is a situation complex clinic [45]. Applied behavior analysis (ABA) are

among the most widespread and potentially effective types of psychological intervention in the clinical management of the disorder and in the reduction of its functional consequences (among which we recall the Early Intensive Behavioral Intervention -EIBI-), the TEACCH method, and the so-called "Eclectic" approaches [46]. Recent reviews have shown rather similar overall rates of effectiveness between the various approaches; in any case, the most useful types of clinical intervention are usually intensive, should be started as early as possible, and need to be continued for quite extended periods of time [47,48]. Currently, therefore, the most effective treatment in autism is psychoeducational intervention. Early treatment, when combined with specific school curricula, parental involvement and adequate medical care, when needed, can greatly reduce the symptoms of autism and increase the child's chances of learning new skills.

With respect to the pharmacological profile, to be applied with patients suffering from autism, it is common ground that the scientific evidence obtained from various researches supports the use of risperidone (in addition with simvastatin) in the short-term and long-term treatments of behavioral problems such as irritability, social withdrawal, hyperactivity and stereotyped behavior in children with autism spectrum disorders [49,50]. Methylphenidate can instead be considered for the treatment of hyperactivity in children or adolescents up to 14 years, with the diagnosis of autism spectrum disorders [51]. Furthermore, the use of selective serotonin reuptake inhibitors (SSRIs) are not recommended for the treatment of autism spectrum disorders in children, as well as the use of secretin or the practice of chelation; however, a recent study has shown that by stimulating the production of the neurotransmitter serotonin in a specific brain region, the nucleus accumbens, social behaviors can be normalized in mice affected by an animal form of autism [52]. Finally, as already mentioned, the latest research has shown a positive outcome in the administration of oxytocin and dopamine [53,54].

Conclusion

Recent research in the neuroscientific field is making a significant contribution to the reconstruction of a pathology with outlines and an etiology that is still not well defined. They add an important piece to the knowledge on the development of the nervous system and are fundamental not only because they contribute to improve the understanding of the data in our possession, but also because they clarify even better the neuropsicobiological bases of autism, giving value to the technical profiles related to the microscopic alterations in specific brain areas, contextualizing in a more defined way also behavioral disorders related to autism spectrum disorders.

References

1. Brugha TS, McManus S, Bankart J, Scott F, Purdon S, et al. (2011) Epidemiology of autism spectrum disorders in adults in the community in England. Arch Gen Psychiatry 68(5): 459-465.

2. Research Laboratories Merck (2008) The Merck Manual quinta edizione, Milano, Springer-Verlag, pp: 2631.

3. Williams DL, Goldstein G, Minshew NJ (2006) Neuropsychologic functioning in children with autism: further evidence for disordered complex information-processing. Child Neuropsychol 12(4-5): 279-298.

4. Zhao X, Leotta A, Kustanovich V, Lajonchere C, Geschwind DH, et al. (2007) A unified genetic theory for sporadic and inherited autism. Proc Natl Acad Sci USA 104(31): 12831-12836.

5. Williams E, Thomas K, Sidebotham H, Emond A (2008) Prevalence and characteristics of autistic spectrum disorders in the ALSPAC cohort. Dev Med Child Neurol 50(9): 672-677.

6. Sandin S, Schendel D, Magnusson P, Hultman C, Surén P, et al. (2016) Autism risk associated with parental age and with increasing difference in age between the parents, Molecular Psychiatry 21(5): 693-700.

7. (2013) Diagnostic and Statistical Manual of Mental Disorders (DSM–5). American Psychiatric Association.

8. Guze (1995) Diagnostic and Statistical Manual of Mental Disorders, 4th (Edn.), (DSM-IV), American Psychiatric Association, DSM-IV, Washington DC 52(8): 1228.

9. American Psychiatric Association (2000) Diagnostic criteria for 299.80 Asperger's Disorder (AD). Diagnostic and Statistical Manual of Mental Disorders, 4th, text revision (DSM-IV-TR).

10. Klin A (2006) Autism and Asperger syndrome: an overview. Rev Bras Psiquiatr 28(S1): S3-S11.

11. Baskin JH, Sperber M, Price BH (2006) Asperger syndrome revisited. Rev Neurol Dis 3(1): 1-7.

12. Klin A (2006) Autism and Asperger syndrome: an overview. Rev Bras Psiquiatr 28 (S1): S3-S11.

13. McPartland J, Klin A (2006) Asperger's syndrome. Adolesc Med Clin 17(3): 771-788.

14. Frith U (1996) Social communication and its disorder in autism and Asperger syndrome. J Psychopharmacol 10(1): 48-53.

15. Fombone E (2002) Prevalence of childhood disintegrative disorder. Autism 6(2):149-57.

16. Visconti P (2003) La terapia di Scambio e di Sviluppo. In: Formica M (Ed.), Trattato di Neurologia Riabilitativa, Cuzzolin Editore, pp: 987-1016.

17. Valnegri P, Huang J, Yamada T, Yang Y, Mejia LA, et al. (2017) RNF8/UBC13 ubiquitin signaling suppresses synapse formation in the mammalian brain, Nature Commun 8(1): 1271.

18. Zhan Y, Paolicelli RC, Sforazzini F, Weinhard L, Bolasco G, et al. (2014) Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. Nature Neuroscience 17(3): 400-406.

19. Amaral DG, Schumann CM, Nordahl CW (2008) Neuroanatomy of autism. Trends Neurosci 31(3): 137-145.

20. Supekar K, Kochalka J, Schaer M, Wakeman H, Qin S, et al. (2018) Deficits in mesolimbic reward pathway underlie social interaction impairments in children with autism. Brain 141(9): 2795-2805.

21. Roberts TP, Khan SY, Rey M, Monroe JF, Cannon K, et al. (2010) MEG detection of delayed auditory evoked responses in autism spectrum disorders: towards an imaging biomarker for autism. Autism Research 3(1): 8-18.

22. Roberts TP, Cannon KM, Tavabi K, Blaskey L, Khan SY (2011) Auditory Magnetic Mismatch Field Latency: A Biomarker for Language Impairment in Autism. Biol Psychiatry 70(3): 263-269.

23. Rizzolatti G, Fabbri-Destro M (2010) Mirror neurons: from discovery to autism. Exp Brain Res 200(3-4): 223-237.

24. Williams JH (2008) Self-other relations in social development and autism: multiple roles for mirror neurons and other brain bases. Autism Research 1(2): 73-90.

25. Wallace GL, Dankner N, Kenworthy L, Giedd JN, Martin A (2110) Age-related temporal and parietal cortical thinning in autism spectrum disorders. Brain 133(12): 3745-3754.

26. Kosaka H, Omori M, Munesue T, Ishitobi M, Matsumura Y, et al. (2010) Smaller insula and inferior frontal volumes in young adults with pervasive developmental disorders. Neuroimage 50(4): 1357-1363.

27. Krey JF, Dolmetsch RE (2007) Molecular mechanisms of autism: a possible role for Ca_2+ signaling. Curr Opin Neurobio 17: 112-119.

28. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA (2005) Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurology 57(1): 67-81.

29. Andrew W Zimmerman (2010) Autism: Current Theories and Evidence - Humana press. Totowa. New Jersey. 2008 Abha Chauhan, Ved Chauhan and Ted Brown - Autism: Oxidative Stress, Inflammation, and Immune Abnormalities. Taylor & Francis Group, CRC Press. New York, pp: 456.

30. Herbert MR (2010) Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders. Curr Opin Neurol 23(2): 103-104.

31. Ruta L, Ingudomnukul E, Taylor K, Chakrabarti B, Baron-Choen S (2011) Increased serum androstenedione in adults with autism spectrun condition. Psychoneuroendocrinology 36(8): 1154-1163.

32. Aneja A, Tierney E (2008) Autism: the role of cholesterol in treatment. Int Rev Psychiatry 20(2): 165-170.

33. Knickmeyer RC, Baron-Cohen S (2006) Fetal testosterone and sex differences in typical social development and in autism. J Child Neurol 21(10): 825-845.

34. Pfaff DW, Rapin I, Goldman S (2011) Male predominance in autism: neuroendocrine influences

on arousal and social anxiety. Autism Res 4(3):163-176.

35. Sarachana T, Xu M, Wu RC, Hu VW (2011) Sex hormones in autism: androgens and estrogens differentially and reciprocally regulate RORA, a novel candidate gene for autism. PLoS One 6: e17116.

36. Andari E, Duhamel JR, Zalla T, Herbrecht E, Leboyer M, et al. (2010) Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. Proc Natl Acad Sci USA 107(9): 4389-4394.

37. Parker KJ, Oztan O, Libove RA, Sumiyoshi RD, Jackson LP, et al. (2017) Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism. Proc Natl Acad Sci USA 114(30): 8119-8124.

38. Gregory SG, Connelly JJ, Towers AJ, Johnson J, Biscocho D, et al. (2010) Genomic and epigenetic evidence for oxytocin receptor deficiency in autism. BMC Medicine 7: 62.

39. Szczurkowska J, Pischedda F, Pinto B, Managò F, Haas CA, et al. (2018) NEGR1 and FGFR2 cooperatively regulate cortical development and core behaviours related to autism disorders in mice. Brain 141(9): 2772-2794.

40. Goldstein S, Ozonoff S (2018) Assessment of Autism Specttrum Disorder, 2th (Edn.), GP The Guilford Press.

41. Yuen RK, Merico D, Cao H, Pellecchia G, Alipanahi B, et al. (2016) Genome-wide characteristics of de novo mutations in autism. NPJ Genomic Medicine 1: 16027.

42. Hazlett HC, Gu H, Munsell BC, Kim SH, Styner M, et al. (2017) Early brain development in infants at high risk for autism spectrum disorder. Nature 542(7641): 348-351.

43. Gilman JT, Tuchman RF (1995) Autism and associated behavioral disorders: pharmacotherapeutic intervention. Ann Pharmacother 29(1): 47-56.

44. Howes OD, Rogdaki M, Findon JL, Wichers RH, Charman T, et al. (2018) Autism Spectrum Disorder: consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. J Psychopharmacol 32(1): 3-29.

45. Howlin P, Magiati I, Charman T, William E, MacLean (2009) Systematic Review of Early Intensive Behavioral Interventions for Children With Autism. Am J Intellect Dev 114(1): 23-41.

46. Callahan K, Shukla-Mehta S, Magee S, Wie M (2010) ABA Versus TEACCH: The Case for Defining and Validating Comprehensive Treatment Models in Autism. J Autism Dev Disord 40(1): 74-88.

47. Howlin P (2010) Evaluating psychological treatments for children with autism-spectrum disorders. Advances in Psychiatric Treatment 16: 133-140.

48. Magiati I, Charman T, Howlin P (2007) A two-year prospective follow-up study of community-based early intensive behavioural intervention and specialist nursery provision for children with autism spectrum disorders. Journal of Child Psychology and Psychiatry 48(8): 803-812.

49. Moazen-Zadeh E, Shirzad F, Karkhaneh-Yousefi MA, Khezri R, Mohammadi MR, et al. (2018) Simvastatin as an Adjunctive Therapy to Risperidone in Treatment of Autism: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. J Child Adolesc Psychopharmacol 28(1): 82-89.

50. Nuntamool N, Ngamsamut N, Vanwong N, Puangpetch A, Chamnanphon M, et al. (2017) Pharmacogenomics and Efficacy of Risperidone Long-Term Treatment in Thai Autistic Children and Adolescents, Basic Clin Pharmacol Toxicol 121(4): 316-324.

51. Sturman N, Deckx L, van Driel ML (2017) Methylphenidate for children and adolescents with autism spectrum disorder. Cochrane Database Syst Rev 11: CD011144.

52. Walsh JJ, Christoffel DJ, Heifets BD, Ben-Dor GA, Selimbeyoglu A, et al. (2018) 5-HT release in nucleus accumbens rescues social deficits in mouse autism model. Nature 560: 589-594.

53. Watanabe T, Kuroda M, Kuwabara H, Aoki Y, Iwashiro N, et al. (2015) Clinical and neural effects of six-week administration of oxytocin on core symptoms of autism. Brain 138(11): 3400-3412.

54. Paval D (2017) A Dopamine Hypothesis of Autism Spectrum Disorder. Dev Neurosci 39(5): 355-360.