THE CHILD WITH AUTISM SPECTRUM DISORDERS (ASDS) : BEHAVIORAL AND NEUROBIOLOGICAL ASPECTS

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ABSTRACT

Introduction: The Autism Spectrum Disorders (ASDs) have onset in the first years of life and are characterized clinically by qualitative impairments in social interaction, communication and a restricted repertoire, stereotyped and repetitive interests and activities. Currently there is a medical consensus on the causes of autism: they should not be psychosocial but should be based in biology, especially in the central nervous system abnormalities caused by both inherited and environmental causes. The aim of this study was to study a sample of subjects with Autism Spectrum Disorders (ASDs) with a wide protocol, including neurophysiological and radiological investigations as well as laboratory investigations in order to investigate the neurobiologic basis of the syndrome.

Methods: The patients group included 34 subjects diagnosed as having ASDs. All were examined with a protocol of investigations (brain MRI; EEG; VEP, ABR; karyotype; evaluation of brain metabolites; antibodies against neurotrophic agents). In order to evaluate and identify the presence and intensity of autistic symptoms have been used the CARS (Childhood Autism Rating Scale) and ADOS (Autism Diagnostic Observation Schedule) tools.

Results and Conclusion: Ninety percent of the subjects had at least one parameter neurobiological disease, the fifty-nine percent have a specific genetic syndrome. This study highlights the different noxae involved in the etiopathogenesis of AD and the percentage that every biological factor has in the development of the autistic phenotype. This study confirms the hypothesis that autism spectrum disorders (ASDs) are a severe neuropsychiatric diseases with strong genetic basis.

Key words: Autism Spectrum Disorder - Behavioral - Neurobiological Aspects - Children.

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Introduction

The Autism Spectrum Disorders (ASDs) have onset in the first years of life and are characterized clinically by qualitative impairments in social interaction, communication and a restricted repertoire, stereotyped and repetitive interests and activities\(^\text{1}\). Although the discovery of autism goes way back to 1943, still there is no absolute theory and convincing to explain the appearance of this disease. Currently there is a medical consensus on the causes of autism: they should not be psychosocial but should be based in biology, especially in the central nervous system abnormalities caused by both inherited and environmental causes. Among the environmental factors hypotheses more consistent from the scientific point of view argue for viral infections such as rubella, herpes or cytomegalovirus. It also reported complications during pregnancy and poisoning. Several other studies show that there is some correlation of hereditary; in some cases they have been identified genetic problems like duplication of chromosome 15, tuberous sclerosis, fragile X, phenylketonuria or neurofibromatosis. Due to the fact that autism is a disorder in which show brain damage, it is logical to think that the same can be caused by several factors, both of environmental origin that genetics. Referring to the neurobiology of autism we find very different data. They were found several anatomical abnormalities in the brain and also at the level of neurotrans-
mitters in the brain. Morant and Mulas presented their theory that: autism is a genetically conditioned disease which manifest anatomical changes in the brain, the neurotransmitters and activity bioelectrical brain.(3). Recent genetic discoveries and those derived from neuroimaging studies suggest that autism is associated with alterations in connectivity during development, impairing the normal process of maturation of neural structures, causing a alteration of functional connectivity (easy connectivity and/or hyperconnectivity) inside neural networks resulting in abnormal synchronization between brain areas critical "association of higher order", responsible for the onset of autism.(5).

Research on the epidemiology and the genetic origin of the ADSs, have shown that the difficulties in the construction of social reciprocity can also be present in individuals of normal intelligence.(4). Currently we talk about a wide spectrum of disorders similar quality but mitigated in various aspects and present even in people with normal intellectual development.(1, 3, 5). Nowadays it is correct use the term autisms or autism spectrum disorders, diseases with similar features but different in terms of etiology, brain areas affected and behavioral manifestations, similar in their structural aspect but different in intensity, quality and quantity.(5). The aim of this study was to study a sample of subjects with Autism Spectrum Disorders (ASDs) with a wide protocol, including neurophysiological and radiological investigations as well as laboratory investigations in order to investigate the neurobiologic basis of the syndrome.

Materials and methods

The patients group included 34 subjects (24 males and 10 females) diagnosed as having ASDs. All subjects were examined with a protocol of investigations including: brain MRI; EEG; VEP, ABR; karyotype and search of the fragile X; serum and urinary levels of serotonin, catecolamines, omovanillic acid, aminoacids, ammonium, lactic acid, creatine kinase, piruvic acid, calcium, uric acid, total proteins, antibodies against neurotrophic agents. In order to assess the intelligence of subjects Wisch-R intelligence scale (Wechsler Intelligence Scale for Children) and WPPSI (Wechsler Preschool and Primary Scale of Intelligence) were used. They highlight harmonies and disharmonies between the different manifestations of intellectual development. In order to evaluate and identify the presence and intensity of autistic symptoms have been used the CARS (Childhood Autism Rating Scale) and ADOS (Autism Diagnostic Observation Schedule) tools. This assessment allows us to strengthen the presence and intensity of the symptoms presented by the child. The scale CARS is compiled on the basis of the observation of the behavior within the unstructured context. The behavior is compared to that of a peer without difficulty. The ADOS is a semi-structured and standardized assessment of communication, social interaction, play and imaginative use of materials for individuals with ASDs. The ADOS consists of standardized activities that allow examiner to observe those behaviors that are important for the diagnosis of autism spectrum disorder in different chronological age and for different levels of development. Through this tool the child's behaviors can be assessed in response to situations and stimulus activities predetermined by the test in order to obtain information on the characteristics of interpersonal and communication. The test is based on an evaluation framework designed to generate interactive situations that provide stimuli at the social level, through play and verbal exchanges. The ADOS includes four different modules depending on the age and level of expressive language of the subject. In all our cases, we used the module 1. In most of the activities of this module, the focus is directed to the use of observation fun toys and other materials are particularly important for children with an age of development under three years. The first module consists of 10 activities (free play, response to name, response shared attention, game bubbles, anticipation of a routine with objects, social smile response, anticipation of a social routine, imitation functional and symbolic feast birthday, snacks). Scores are organized into five main groups: “A. Language and Communication”, “B. Reciprocal social interaction”, “C. Game”, “D. Stereotyped behaviors and restricted interests” and “E. other vices”.

Results

The average age of children was five years and five months (Table 1). Parents of all subjects were non-consanguineous and the stories of the children were negative for neurological and psychological disorders in 36% of cases and were positive in 64% of cases. While 68% of subjects had a good neonatal adaptation, 32% presented a not good adaptation. The biological study revealed alterations of the various parameters considered in a variable percentage
between twenty-four subjects of the group examined. Ninety percent of the subjects had at least one parameter neurobiological disease; the fifty-nine percent have a specific genetic syndrome. In thirty-five percent of the subjects were recorded EEG changes; sixteen percent has a partial epilepsy. The study of visual evoked potentials have emerged profiles altered in eighteen percent of subjects; while the auditory evoked potentials were altered are in four percent of the subjects examined. Neuroimaging abnormalities detected are variable as to the type and location. In particular, have been detected: increase in the volume in cerebellar two percent, hypoplasia of the corpus callosum in four percent of the subjects, reduced the extent of the hippocampus and amygdala in six percent, abnormalities of the frontal lobe and the parietal and temporal lobes in fourteen percent. High levels of serotonin in the blood are present in about twenty-five percent of subjects. There were no other alterations in biochemical parameters.

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Table 1: Characteristics of observed subjects.

The average score at Wisch-R was 70.6 for verbal IQ and 76.0 for performance IQ (Table 2). The child with autism spectrum disorder (ASDs): Behavioral and neurobiological aspects

As regards the CARS, subjects showed an average overall score of 29.6. The subjects all showed behavioral problems related to all areas commonly deficient in individuals with autism spectrum: social interaction; verbal and non-verbal; repertoire of activities and interests.

With concern to ADOS, children showed an average score for language and communication equal to 3.3 and echolalia has limited use of gestures restrictive. Reciprocal social interaction got an average score of 5.8; children made a limited use of visual contact and did not show proper integration to request certain objects. In the same subjects showed an average score of 3.1 and they did not use the objects as symbolic substitutes. Regarding stereotyped behaviors and restricted interests children got an average score equal to 3.8 and they had a particular interest in some materials, presented some stereotypies of hands and none self aggressive behaviors.

By the administration of these scales was confirmed the presence of an autism spectrum disorders in all subjects.
Discussion

The Autism Spectrum Disorders (ASDs) are characterized by severe and pervasive impairment in two areas of development: that of communication skills and social interaction (deficits in communication of social and emotional reciprocity, in non-verbal communication used for social purposes, in the creation and maintenance social bonds properly to the general level of development) and the area of interest and activities (stereotyped movements, speech or objects; excessive adherence to routines, rituals motor or verbal and/or resistance to change; fixation for special interests or narrow abnormally in duration or intensity; hyper- or hypo responsiveness to sensory stimuli or unusual interest in particular details of the environment)\(^1,5\).

Research on the epidemiology and the genetic origin of the ADSs, have shown that the difficulties in the construction of social reciprocity can also be present in individuals of normal intelligence\(^6\). The diagnosis usually is not formalized before 3-4 years of age (although you can recognize the signs of risk for a disorder of communication and social interaction already at 18 months) and its definition is already considered reliable 24 months if it conducted by experts in recognizing the early signs of dysfunction socio-communicative. Epidemiologic studies report an ASD prevalence of approximately 3 to 6/1000, with a male to female ratio of 3:1. The data we receive from the most recent studies in the United States attest to the prevalence of ASDs than 1 in 110 children and in most cases can be demonstrated a genetic cause\(^6,7\).

The discovery of a multitude of genes (and their mutations/genetic variants) involved in neurodevelopmental processes and the technological advancements in imaging the brain with positron emission tomography (PET) and magnetic resonance structural (IRM) and functional (fMRI) have had a profound impact on our understanding of the neurobiological basis of autism through the study, the anatomical and functional connectivity of the brain, greatly improving the ability to examine the neural substrates of cognitive processes\(^1,4,6\).

Etiology of autism is very diverse and epidemiological data have shown the presence of inheritance in the etiology of autism. Epidemiological data have shown the presence of inheritance in the etiology of ASDs. In various researches it has been found that 4.2% of siblings of individuals with ASDs are affected by autism, a rate that is fifty times higher than the general population; the observation that parents, siblings and relatives often show personality traits, though less severe, due to the social deficits typically observed in autistic probands\(^3,12\), provide convincing evidence that genetics plays a key role in the etiology of this disease\(^3,13\). Twin studies, demonstrate a high degree of agreement, especially in monozygotic, in monozygotic (in cases where there is no other comorbidities) it has been revealed about 69% agreement in the manifestations of the disease, compared with 5% in the case of fraternal twins; Identical twins with simple intellectual disabilities, compared to twin autistic, then tend to develop difficulties in social mutual\(^5,14\). Compared with the risk of ASDs in the population, these two data show heritability of about 90%, by far the highest among all developmental disorders\(^9\). The comorbidity of autism with various diseases has corroborated the hypothesis of a genetic implication. Genetic factors are therefore multiple, each case on its own is rare, except for the fragile X syndrome\(^15-20\).

Recent findings have identified a multitude of genes, involved in maturational processes of the development of neural connections, which confer risk for autism; However it is not clear whether the disorder follows a rare genetic mutations or rare multigene interactions of common genetic variants\(^5,21-23\). Common genetic variants have been found on chromosome 5 and code for proteins of neuronal cell adhesion, cadherin 9 (CDH9) and cadherin 10 (CDH10) and may be responsible for 15% of all cases of autism\(^23\). It seems that an important role in autism is due to several members of gene families of contactina (Cntn) and associated protein contactina (CNTNAP), which play an essential function as adhesion molecules for the formation and plasticity of neural networks\(^24\). Chromosomal variations, including the copy number variation (CNV), appear to be responsible for 5-10% of cases of ASDs\(^25\). Rare genetic risk variation identified to date, in contrast, has a very substantial effect on individual risk. Recent whole-exome sequencing analyses of large ASD cohorts have expanded the repertoire of known genes harboring ASD-linked mutations that were previously identifiable only by traditional genetic approaches and targeted sequencing\(^26\). At this point, it is clear that rare microscopically detectable chromosomal rearrangements, submicroscopic deletions or duplications (CNV or smaller structural variation), single-nucleotide variation (SNV) and small deletions and
duplications (indels) all contribute to risk\(^\text{(26)}\). Autistic behaviors can also manifest as part of genetic syndromes, including monogenic disorders or syndromes caused by chromosomal abnormalities\(^\text{(27)}\).

The wide phenotypic variability of the ASDs likely reflects the interaction of multiple genes within an individual’s genome and the existence of distinct genes and gene combinations among those affected. Data from whole-genome screens in multiplex families suggest interactions of at least 10 genes in the causation of autism. Thus far, a putative speech and language region at 7q31-q33 seems most strongly linked to autism, with linkages to multiple other loci under investigation\(^\text{(28)}\). Cytogenetic abnormalities at the 15q11-q13 locus are fairly frequent in people with autism, and a “chromosome 15 phenotype” was described in individuals with chromosome 15 duplications. Among other candidate genes are the FOXP2, RAY1/ST7, IMMP2L, and RELN genes at 7q22-q33 and the GABA(A) receptor subunit and UBE3A genes on chromosome 15q11-q13. Variant alleles of the serotonin transporter gene (5-HTT) on 17q11-q12 are more frequent in individuals with autism than in nonautistic populations. In addition, animal models and linkage data from genome screens implicate the oxytocin receptor at 5p25-p26\(^\text{(29)}\).

Several genes predisposing to autism spectrum disorders (ASDs) with or without epilepsy have been identified, many of which are implicated in synaptic function\(^\text{(29)}\). It is reported Q555X a mutation in synapsin 1 (SYN1), a gene encoding X-linked to a specific phosphoprotein of the neurons involved in the regulation of neurotransmitter release and sinaptogenesis. Here we report to Q555X mutation in synapsin 1 (SYN1), an X-linked gene encoding for a neuron-specific phosphoprotein implicated in the regulation of neurotransmitter release and sinaptogenesis\(^\text{(29)}\).

This nonsense mutation was found in all affected individuals from a large French-Canadian family segregating epilepsy and ASDs. Additional mutations in SYN1 (A51G, A550T and T567A) were found in 1.0 and 3.5% of French-Canadian individuals with autism and epilepsy, respectively\(^\text{(29)}\). The majority of these SYN1 mutations were clustered in the proline-rich D-domain which is substrate of multiple protein kinases. When expressed in synapsin 1 (SynI) knockout (KO) neurons, all the D-domain mutants failed in rescuing the impairment in the size and trafficking of synaptic vesicle pools, whereas the wild-type human SynI fully reverted the KO phenotype. Moreover, the nonsense Q555X mutation had a dramatic impact on phosphorylation by MAPK/Erk and neurite outgrowth, whereas the missense A550T and T567A mutants displayed impaired targeting to nerve terminals\(^\text{(29)}\). These results demonstrate that SYN1 is a novel predisposing gene to ASDs, in addition to epilepsy, and strengthen the hypothesis that a disturbance of synaptic homeostasis underlies the pathogenesis of both diseases\(^\text{(29)}\). Through further analysis of patients with autism or epilepsy, other mutations in the same gene have been identified respectively in the 1% of autistic patients and in 3.5% of patients with epilepsy, showing how SYN1 is essential in the genetic predisposition to the two diseases\(^\text{(29)}\).

Neuroimaging studies, in concert with neuropathological and clinical research, have been instrumental in delineating trajectories of development in children with ASD. Structural neuroimaging has revealed ASD to be a disorder with general and regional brain enlargement, especially in the frontotemporal cortices, while functional neuroimaging studies have highlighted diminished connectivity, especially between frontal-posterior regions\(^\text{(30)}\). A large number of researches have detected three types of alterations in the brain stem and cerebellum, in the limbic system which includes the amygdala and the cerebellum, and in the cortex. As for the brain stem and the cerebellum, anatomical studies have shown a significant absence of nuclei in the first region (for example the facial motor nuclei olive and higher) with relative decrease of cell density\(^\text{(30-31)}\). MRI studies have identified an increase in the volume of the cerebellar white matter of 40% in autistic subjects compared to the control group; important anomalies also involve structures such as the cerebellum, the amygdala and the hippocampus\(^\text{(32)}\).

Some studies suggest the presence of abnormalities of the processes that mediate brain development early in the clinical course of the disorder. In fact, recent researches indicate the amygdala seems to go through a period of expansion that continues throughout early childhood, then adolescence, does not differ significantly\(^\text{(30-32)}\). Abnormalities in this area could be the basis of explanations of some symptoms of the disorder such as anxiety, deficits in social interaction and communication, deficits in the recognition of facial expressions. Among the brain areas affected also
includes the frontal lobes, the superior temporal cortex, and parietal. The frontal and prefrontal lobes are associated with executive functions, to the attention of visual and implications of the theory of mind. Abnormalities in the frontal lobes were taken into account, depending on their involvement in autistic symptoms, particularly the social isolation and the inability of the party to act generalizations. An abnormal activation of these regions were found in tasks of understanding of stories, in the processing of social cues and visual search of hidden items. One of the theories more shared on neuropathology autistic is that according to which the brain would suffer a growth phase early in the first period of life, followed by a slowdown in growth\(^{30}\).

Further studies show an association between increased brain volume with increased white matter in the frontal lobe. One other case that has aroused widespread interest, regards the anomalies in the brain cytoarchitecture in particular in the number and scope of the columnar structures of the cortex; in autistic these mini columns are more numerous and are smaller than the neurons that make and are more tangled with each other than to those with typical development\(^{30-34}\). In summary, the studies on brain structure by IRMS-MRI and DTI in autism show numerous anatomical changes suggestive of a pervasive disorder in neuronal networks during the early stages of development\(^{3,36}\) and suggest abnormal trajectory of brain development, characterized by accelerated and excessive growth of the brain, with obvious signs of increased cortical thickness, atypical patterns of arrangement of the turns of the cerebral cortex, abnormalities of the gray matter and white matter fiber tracts, which appear altered due to a abnormal water content and the myelination process which appears late and protracted. These anomalies, widely present in several brain regions, suggesting that autism is a disorder widely distributed, not confined to a single region\(^{39}\).

The neuro-anatomical abnormalities, observed in autism during the excessive growth of the brain, can promote defects in neuronal patterning and wiring, resulting in defective cortical interactions, suggesting that in autism there is a altered brain connectivity ("disconnectivity") with diffuse connective tissue disorders that affect many cortical areas. In particular, studies with IRMS suggest that people with autism are characterized by decreases in long-range connections and increases in short-range connections\(^{3,30,37}\). The diverse and specific neuroimaging findings may represent potential neuroendophenotypes, and may offer opportunities to further understand the etiopathogenesis of ASD, predict treatment response, and lead to the development of new therapies\(^{30}\). Among these last, appropriate there are several treatments to improve the quality of life of patients well as the direct contact with nature and enjoyment of the rural landscape thanks also to the multifunctional role of farms\(^{1,38-40}\).

A further attempt to explain autism is based on the presence of abnormalities at the receptors or neurotransmitters serotonin, dopamine, oxytocin and vasopressin. It was in fact recorded a clear reduction in the synthesis of serotonin in children with ASDs in the frontal areas, while there has been an increase in serotonin in the areas of the cerebellum\(^{41}\). The studies of serotonin, dopamine, epinephrine, norepinephrine and endogenous opioids show that these neurotransmitters have mutual interference in metabolism and receptor. The dopamine system, with the influences of other neurotransmitters, carries out its main activity on the mesolimbic system, meso-cortico-frontal and nigrostriatal. Through this network of facilities will exercise the functions of attention, perception, association, intention, motor skills, communication, emotion, behavioral and perceptual constancy. A dysregulation of the dopaminergic system may explain the symptoms of people with ASDs, such as isolation, perceptual and behavioral abnormalities.

Even non-genetic causes may play a role in the etiology of ASDs. Are called upon several factors above all prenatal infections contracted during pregnancy, the postnatal period seems an important role to play it herpetic encephalitis. Epidemiologic studies indicate that environmental factors such as toxic exposures, teratogens, perinatal insults, and prenatal. Among the prenatal factors are reported some infectious diseases (congenital rubella, cytomegalovirus, toxoplasmosis, congenital syphilis), the alcoholism of the mother. Even deficits of blood perfusion during pregnancy can cause brain damage responsible for the symptoms of autism. Among the perinatal factors can have an influence hypoxic haemorrhagic syndrome, while among the postnatal factors including infectious (especially encephalitis herpetic), traumatic, toxic and vascular acting in the first three years of a child's life\(^{26-30}\). We can therefore say that the etiology of ASDs is very heterogeneous.

The current knowledge provided by a large number of studies on the brain (anatomical, histological, physiological and functional), in addition to
genetic, indicate that autism is a neurobiological disorder of development. The data reported here furthermore, confirm that ASDs correspond to an atypical behavioral phenotype expression of a cerebral dysfunction with heterogeneous etiology.

Conclusions

It can be said that autism spectrum disorders collect a set of pathologies characterized by a general difficulty in establishing interpersonal relationships, problems caused by neurodevelopmental, altering in the first years of life the ability to relate with others, cause different effects of cognitive, affective and behavioral\(^5,22-42\). Autism spectrum disorders (ASDs) are a severe neuropsychiatric diseases with strong genetic underpinnings\(^5\). However, genetic contributions to autism are extremely heterogeneous, with many different loci underlying the disease to a different extent in different individuals. Moreover, the phenotypic expression (i.e., “penetrance”) of these genetic components is also highly variable, ranging from fully penetrant point mutations to polygenic forms with multiple gene-gene and gene-environment interactions\(^42\).

Furthermore, many genes involved in ASD are also involved in intellectual disability, further underscoring their lack of specificity in phenotypic expression\(^42\). Analysis of the data shows significant correlations between organ damage and severe clinical pictures of ASDs. It should be noted that beside syndromes secondary to genetic disorders, there are clinical situations where it is demonstrably certain biological origin, such cases have a better cognitive structure. In our study ninety percent of the subjects had at least one parameter neurobiological disease, the fifty-nine percent have a specific genetic syndrome. This study highlights the different noxae involved in the etiopathogenesis of AD and the percentage that has every biological factor in the development of the autistic phenotype. This study confirms that the hypothesis autism spectrum disorders (ASDs) area severe neuropsychiatric diseases with strong genetic basis.

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