AUTISM, AN OVERWHELMING CONDITION: HISTORY, ETIOPATHOGENESIS, TYPES, DIAGNOSIS, THERAPY AND PROGNOSIS

Ioana Cristina Amihăesei, Elena Ștefanachi
University of Medicine and Pharmacy “Grigore T. Popa” - Iași
Faculty of Medicine
Discipline of Histology

AUTISM, AN OVERWHELMING CONDITION: HISTORY, ETIOPATHOGENESIS, TYPES, DIAGNOSIS, THERAPY AND PROGNOSIS (Abstract): Autism is defined as a neurologic developmental disorder affecting brain and behavior, becoming usually apparent before 3 years of age, with stable evolution and no remission. No neurologic morphologic abnormality was associated with the disease. Several types of disease being described, autism is part of a larger spectrum known as autism spectrum disorders (ASD), or pervasive developmental disorders (PDD). The disease was first described long before it was defined and it has received its modern name. Main cause in the development of autism is considered to be genetic, up to 90%. However, environmental factors could be incriminated, sometimes. The five types included in ASD are: Asperger syndrome, pervasive developmental disorder-not otherwise specified (PDD-NOS), typical autism, Rett syndrome and childhood disintegrative disorder (CDD). The classical triad of symptoms includes: social interaction impairments, communication impairments and repetitive, stereotype behavior. Diagnosis is based on interview of the parents and specialized observation of the suspected children. Main tools used in therapy are the family and the educational system. Well established, specialized programs of therapy were developed in time. Prognosis of autism is severe, since no cure is possible; nevertheless spontaneous recoveries do occur, in some cases. Key words: AUTISM, AUTISM SPECTRUM DISORDERS (ASD), PERVASIVE DEVELOPMENT DISORDERS (PDD)

Some cases were described long before the disease has received its name and its characteristics were established. The earliest well-argumented case of autism is that of Hugh Blair of Borgue, which is described in a law report from 1747, where his brother tried to revoke Blair’s marriage, in order to obtain the inheritance.

The Swiss psychiatrist Eugen Bleuler first used the word autism (from Latin, autismus) to describe symptoms of schizophrenia. In fact, the word is deriving from the Greek autós (self) and was used to define abnormal self-admiration and autistic isolation of the patients in their fantasies, in which outside influence became intolerable (1).

In 1938, Hans Asperger of the Vienna University Hospital used the term autistic psychopaths in a lecture, thus the term autism found its modern sense. Asperger then described the entity now known as the Asperger syndrome, although the condition was not recognized as a separate diagnosis...
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till 1981.

In its modern sense, in English language, the term autism was first used by Leo Kanner (Johns Hopkins Hospital), when he referred in 1943, to „early infantile autism”; he was then describing 11 cases of autism. His description was so accurate that is still typical for the autism spectrum disorders (2).

In the late 1960s, autism was recognized as a syndrome with life-long duration, distinct from other development disorders, such as mental retardation or schizophrenia; it was also widely accepted the benefit brought up by the active therapy programs. Although in 1970, the genetic etiology of the autism it was still not clear, now the disease is considered one of the most heritable of all psychiatric diagnoses (3).

ETIOPATHOGENESIS

The genetics of autism is complex and is not yet clear if autism can be explained by genetic mutations, or by peculiar multigene interactions of common genetic subtypes. Its complex features develop from interactions between multigene, environment and factors which are able to influence the gene expressions. Genetic factors are estimated to represent over 90 %; in the genesis of autism. Studies on twins have shown that many of the non-autistic siblings do manifest however, social and/or learning disabilities (4).

The risk of hereditary transmission in the families with autistic individuals was estimated at about 30 %. Linkage and association genetic analyses were un conclusive. It seems that more than one gene is involved; more such genes were located, but the specific mutations could not be identified. Recently was accepted that several different causes might finally lead to autism, as it is the case with the mental retardation, when different types of brain abnormalities would have the same final result (5,6).

The number of autism diagnoses increased dramatically, especially after 1980, and even more in 1990 and 2000. It seems that this is due, at least in part, to modification of the diagnosis procedures. It is not yet established if the prevalence of the disease increased in the same measure (2008 – 11.3 children/1000, 2012 – 20 children/1000, in U.S.A) (7).

Environmental factors may rather aggravate than trigger, the development and the evolution of the disease. Among such factors, considered to be involved are: infectious diseases, solvents, heavy metals, phthalates and phenols from plastic products, drugs, pesticides and vaccines (8).

In a certain way, autism seems to be directly opposite to schizophrenia, since in autism are expressed paternal genes which are regulating the overgrowth of the brain, while in schizophrenia are expressed maternal genes, which are inducing the underdevelopment of the brain (9).

Advanced paternal and maternal age at the time of the procreation are also incriminated in the genesis of the autism. From the point of view of the paternal age, two theories are suggested: mutations accumulated in time, which would affect the quality of the spermatozoa, and the autistic traits of personality, which would determine such male individuals to marry and procreate later; the two hypotheses are in fact completing each other. It is difficult to appreciate to what extent, paternal or maternal age, or both are important in the genesis of the disease (8).

Prenatal viral infections which are clearly involved are rubeolic and cytomeg-
alic virus infections. The rubeolic congenital syndrome is the most striking proof of the involvement of non-genetic factors in the genesis of the autism. Teratogens, such as thalidomide, valproic acid/misoprostol are involved as well, in the development of the disease. The alcoholic fetal syndrome is also increasing the risk for autism.

The gestational diabetes was found as a significant risk factor, in a 2009 study, demonstrating a risk for having an ASD child, two times higher than in the case of the non-diabetic mothers. In a study conducted in april 2012, metabolic syndrome, associating diabetes, obesity and high blood pressure was more frequent among mothers of ASD children; in the same study, the interrelation between obesity and pregnancy, as a single risk factor for having children with autism was also found strongly positive (7,8).

The opiate theory was advanced in 1979 by Jaak Panksepp, who noticed that small amounts of opiate substances injected in young laboratory animals, produced symptoms similar to those found in autism. He postulated that a digestive abnormality present at birth, could lead to the transformation of the gluten and of the caseine into opiate substances – gliadorphine and caseomorphine, which would interfere with the capacity of sensory reception in these children. Thus, they will show a need for constant stimulation, at the visual level (obsession for rotating objects, characteristic movement of the fingers in front of the eyes, etc.), auditory level (screaming), vestibulare level (swinging, spining, rotatory movements) and tactile level (hand clapping, self-injury) etc., which would explain at least partially, the symptoms of autism. Yet, the scientific data are not validated to exclude these type of nutrients from diet (10, 11).

Another factor incriminated in the development of autism is the prenatal exposure to important stress. The theory of the fetal testosterone is stating that the increased levels of testosterone in the amniotic fluid would force the brain development toward an increase in the complex analysing and synthetic capacities, in the detriment of the communication abilities and empathy (an overdevelopment of the so-called „male traits” and a decrease of the „female traits” of personality); the theory was controversial and contradicted by other studies. Other perinatal incriminated factors are: the small birth weight, the gestational age and hypoxia at birth. Vaccines were incriminated, especially because numerous parents became aware of the autistic symptoms of their children, concomitantly with a routine vaccination. An impressing number of well-validated studies have infirmed this wrong belief (12, 13).

Pathophysiology is supporting the influence of the amygdala neurons which are involved in the development of the social skills and in the capacity to learn social behavior patterns, and the involvement of the noradrenergic system of the loccus ceruleus, a neuronal system known to be involved in excitation and attention, and thus influencing the learning abilities and the capacity to adapt to the environment. The pathophysiologic theories are involving the cortical structures and their interrelation with behavior (14).

The overdevelopment of the brain of the autistic subjects early after birth would be responsible for an increased number of neurons, an overdevelopment of the synapses in certain key cortical zones, an unbalanced functioning of the neuronal excitatory, versus inhibitory networks. The ab-
normal development of brain synapses is involved as well in the genesis of the epilepsy, thus explaining the frequent association between the two conditions (15).

The theory concerning the mirror neuronal system: this system is activated when a laboratory animal is achieving a task, or is observing another animal achieving the same task. This system would be involved in the capacity of imitating activities, intentions and emotions, through the observation of other individuals. The abnormal development of the mirror neuronal system would interfere with the capacity of imitation, which is important in creating behavioral patterns. The delay in the activation of the mirror neurons was noticed in the Asperger syndrome (16).

A reduced functioning of the deficit neuronal network was also incriminated in the pathogenesis of autism; this network is involved in social and emotional processing, and consequently, in attention and concentration abilities. It has extended connections with the excitatory neuronal networks and it seems that in autism the two networks are not efficiently interconnected, with a deficit in the capacity to rapidly change one circuit, for the other; this could be responsible for a disorder in the capacity of thinking about the self. In ASD individuals was evidenced a peculiar type of signals in the cingulated cortex, in an imagistic study from 2008. The theory of the reduced interconnections is presuming the presence in autism of an overdevelopment of the neuronal interconnections, but which are underfunctioning and with a synchronization deficit, with an excess of low-level processing. In autism are present reduced functional connections between the frontal lobe and other cortical areas. Imaging studies and brainwave studies which have analyzed cortical reactions according to the events the subject had been exposed at, showed the preference of ASD subjects for the non-social stimuli (17).

**TYPES**

Autism spectrum disorders are including five types of autistic developmental disorders.

Asperger syndrome is the most frequent and fortunately the least severe form of autism. It is characterized by disabilities of social interaction and communication. Usually, the subjects do not accept changes in the daily routine and they show a form of learning disability. Motor skills of these subjects are underdeveloped and they are clumsy: they show usually a hypersensitivity for powerful visual and auditory stimuli. Frequently such subjects are intelligent, with high IQ scores, and they may demonstrate a peculiar talent in a domain, in which they are unusually gifted. They have the habit to learn everything about a single subject in which they became obsessively interested, and afterwards they spoke continuously only about this subject. Sometimes, Asperger syndrome and high functional autism are superposed, although this is not clearly established by the specialists. Adults with the diagnosis of Asperger syndrome are at higher risk for the development of anxiety and depression (18).

Pervasive Developmental Disorder not otherwise specified (PDD-NOS). The large majority of the ASD cases are receiving this diagnosis. Usually, these subjects show autistic symptoms more severe than the Asperger syndrome, but they do not meet entirely the diagnosis criteria for typical autism. In such cases the diagnosis is that of PDD-NOS. These patients show im-
pairment of the social function, language abilities better developed than in the typical autism, but not so good as in Asperger syndrome and fewer repetitive behaviors, than in the Asperger syndrome, or typical autism. The disease usually has a later age of development (19).

Typical autism is characterized by clear diagnosis criteria; social function and language abilities are severely impaired and repetitive behaviors are characteristic. Such cases frequently associate mental retardation and convulsive symptoms.

Rett syndrome is affecting almost exclusively the female sex; it is very rare – 1/10-15,000 children. Usually at an age between 6 months and one year and a half, the child cease to respond to social stimuli, a characteristic hand grasping reflex is appearing and the language abilities are rapidly lost. Motor coordination problems may sometimes evolve severely. The syndrome is the result of a single gene mutation, which is not inherited, but the result of the hazard (20).

The childhood disintegrative disorder (CDD) is the most severe form of the autism spectrum disorders, fortunately also the rarest of all. After a period of normal development, usually between 2 and 4 years of age, such children are rapidly losing social, intellectual and language abilities. Frequently, a convulsive disorder is associated and the severe symptoms cannot be recovered. Male sex is more often affected; less than 2 children/100,000 affected by autism spectrum disorders are developing this syndrome (19, 20).

**DIAGNOSIS**

The diagnosis of autism is based upon the classical triad of symptoms: social development impairment, communication disabilities and the repetitive, stereotype behavior. Other symptoms, such as atypical alimentation are frequent as well, but are not essential for the diagnosis.

It is important to stress, the fact that the common symptoms of ASD are present in the general population, without frequent association, and there is no clear border to separate the severe pathology and the ordinary personality traits (21).

The social function impairment is the most striking characteristic of the disease, distinguishing it from other syndromes. These children are smiling and are looking at others more rarely, when they are called by their name. A striking characteristic is that they establish much more rarely visual contact with the others. At 3-5 years of age, they show a poor understanding of the social activities and a reduced capacity to spontaneously contact other people, to imitate, to respond emotionally and to infer the emotional estate of other people.

Communication impairment is affecting 1/3, up to ½ of the autism cases, in such a degree that these subjects do not develop communication skills enough to satisfy their usual needs. In the first year of life delayed babbling, unusual gestures and vocal manifestations are common. They ask more rare different things, they manifest echolalia and the capacity to point or to indicate something, in order to communicate is constantly affected. Autistic subjects show impairment of the complex, abstract and deductive language, proved by poor results at such tests.

The repetitive behavior is classified under The Repetitive Behavior Revised Scale of 2007: stereotype movements (hands flapping, body swinging etc.), compulsive flapping, body swinging etc.), compulsive be-
position); resistance to change, ritual behavior, restrictive behavior (obsession for one game, one toy or one TV program etc.); self-injury is reported to affect approximately 30% of the autistic children (22).

Other symptoms are including sensory abnormalities (more often hypo reactivity), motor impairment (in coordination, reduced muscular tonus), alimentary behavior abnormality (affect up to ¾ of the cases, for that it was once used as a diagnosis criterion; selectivity is the most frequent problem, but ritual at table and food refusal are also common).

Imagistic techniques, MRI and diffusion tensor imaging are used to identify characteristic features for autism, visible on brain scanning.

Important clues for the diagnosis are:
- no babbling till 12 months
- no gesture till 12 months (like to point with a finger)
- no word till 16 months
- no two words proposition (spoken spontaneously and not echolalia) till 24 months
- any regress in what concerns social or language skills, at any age of the child

Diagnosis standards impose at least 6 symptoms, including at least two symptoms of the quality of social interaction, at least one symptom of language disability and at least one of repetitive and restrictive behavior.

Diagnosis instruments that are frequently used are: the Autism Diagnosis Interview Revised, which is a partially structured parent interview and the Autism Diagnosis Observation Schedule, which uses observation and interaction with the child. The Childhood Autism Rating Scale is used in specialized clinic environment, to evaluate the severity of autism through children observation (23).

Differential diagnosis includes the mental retardation, auditory problems, language impairment syndromes, as the Landau-Kleffner syndrome, which can be diagnosed on EEG.

Although an early diagnosis is important for the initiation of the therapy and good chances of recovery, unfortunately this is rarely done in practice (25).

A 2009 American study showed that the ASD diagnosis was established at an average age of 5.7 years, which is far below the recommendations (5). There are cases not diagnosed till adult age, and also cases that are over diagnosed based on uncertain symptoms (21).

Frequently associated comorbidities are: mental retardation (reports are ranging from 25 to 70%, a large variation reflecting the difficulty of a correct evaluation of the intelligence of the autistic individuals); anxiety is common among autism spectrum disorder subjects, there are studies which report a frequency of up to 84% of the autism cases; epilepsy, metabolic syndromes (phenylketonuria), ADHD (attention deficit and hyperactivity disorder) Tourette syndrome are also commonly associated in the ASD patients. Sleep troubles are affecting approximately 2/3 of the autistic patients, representing a reason for initiation of therapy, besides the autism symptoms (23, 24, 25).

**THERAPY**

Main goals of the therapy of autism are to diminish the deficits associated with the disease, and to relief the stress endured by the family, as well as the increase of the life quality and the degree of autonomy of the patients.

A standard therapy does not exist, the
treatment is addressed strictly to the needs of the respective child. Main resources used in the therapy are the family and the educational system. Studies which tried to evaluate the efficiency of different therapeutically methods were inconclusive; however, the psychosocial methods used do show positive effects, suggesting that whatever form of therapy is preferable than none. The applied therapies are improving the adaptive capacity and are decreasing the severity of the symptoms and of the behavior troubles. Most used methods are: the Applied Behavior Analysis (ABA), developmental models, structured learning techniques, speech therapies, social functions therapy and occupational therapy (26).

The opportunity of including ASD subjects with different degrees of severity in the mass educational system is still debated. Many types of medications are used; most frequent antidepressants, stimulatory drugs / psychotropes and antipsychotics. Besides antipsychotics, there are few studies to support the safety of the use of such medications, in autism. The risk of atypical reactions and the high risk of development of side effects are difficult to estimate, in the case of autistic individuals. Till this moment, there is no known drug capable to cure or to diminish the symptoms of autism (27, 28).

In time, numerous unconventional therapies were used in the treatment of autism, such as: acupuncture, antifungal therapy, art therapy, the Denver model, therapy using dolphins, aerobics (interactive computer programs), facilitated communication, music, contact therapy, homeopathy, neuro-feedback, rhythms therapy, yoga etc (19).

**PROGNOSIS**

Autism is not curable; spontaneous recoveries may occur, revoking the autism diagnosis. The recovery may appear sometimes after intensive therapy, but not always. The reported rates of recovery in U.S.A. are situated between 3 and 25 % of the total number of cases. Most autistic children do learn to speak around 5 years of age, some earlier, but some later.

Most ASD adults tend to manifest milder symptoms, than during childhood. Studies to evaluate the evolution of the ASD subjects, above medium age do not exist.

Usually, learning to speak before age of six and an IQ score above 50 are meaning a better future potential.

Different studies show that a high level of autonomy was reached in 4-12 % of the cases. At the opposite pole, 12 % needed hospitalized specialized care, all lifelong. The large majority (46 %) needed continuously specialized residence and achieved only limited autonomy (20).

The costs of autism are very important; in U.S.A., a child born in 2000, needs for his life-duration 3.99 million dollars (adjusted according to the inflation rate for 2013) (7, 29).

**REFERENCES**