SYMPTOMS, CAUSES, EPIDEMIOLOGICAL DATA, AND COEXISTING DISEASES IN PATIENTS WITH AUTISM SPECTRUM DISORDERS

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S u m m a r y. An expression of frustration and confusion, there are outbursts of aggression that can be misinterpreted as a signal of hostility towards the environment. Some of autistic children (about 10%), despite disorders in the development of the nervous system, can present surprising abilities, usually limited to one domain, which are equal to or outweigh the potential of a normal individual. This is called 'savant syndrome'. The phenotypically complex syndromic forms of autism are characterized by coexisting clinical conditions such as congenital defects and dysmorphisms, microcephaly, macrocephaly and other changes. The classification and nomenclature were even more complicated when the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) was published. Diseases from autistic spectrum were counted as one separate group, which reflected the agreement between researchers. The classification, diagnosis, and causes of the observed increase in ASD prevalence still cause a lot of controversy. Currently, genetic factors are the mainstream of research interests as they are perceived as one of the key causative factors.

K e y w o r d s: autism spectrum disorders, symptoms, epidemiology

INTRODUCTION

Observations and interviews with autistic patients show that their perception is either overdeveloped or shows insufficient sensitivity to the reception of incoming sensory stimuli. The nervous system does not process sensory stimuli in the right way, and patients feel overwhelmed by excess emotions or confused because of insufficient neuronal stimulation. In response to unsynchronized random nerve signals, patients manifest unusual behavior, trying to reduce excessive excitement, or,

in the case of insufficient inflow, compensate for reduced stimuli sent to the nervous system [32].

SYMPTOMS, CAUSES, AND COEXISTING DISEASES IN PATIENTS WITH ASD

As an expression of extreme reaction, they can also 'shut themselves in' by disabling one or more sensory functions in a desperate attempt to stop the excessive inflow of sensory information. Often, as an expression of frustration and confusion, there are outbursts of aggression that can be misinterpreted as a signal of hostility towards the environment. This phenomenon defined as sensory overload was observed and described by many authors (Lindsley, 1961, Lipowski 1975). How overwhelming it must be for a small patient is evidenced by the fact that US intelligence recognized the methods that bring prisoners to sensory overload and used them as a torture during interrogations (Streatfeild 2007) [5].

In some cases, the nervous system of autistic patients receives so little information that they are unable to sense communication with their own body. When this situation arises, especially in the case of simultaneous stimuli perceived as an imminent threat, they develop flutter of the hands or swaying of the body as a manifestation of an attempt to calm down and regain a sense of mental homeostasis. These symptoms referred to as sensory deprivation were studied in great detail (Schechter et al., 1969; Ornitz 1974; Harrison, Newirth, 1990) [6], and also used by the CIA during interrogations (CIA's 1983 Human Resource Exploitation Training Manual - HRETM; CIA 1983, p. K-1).

Autism is a disease of the nervous system, which most often manifests itself in childhood and affects the entire life of the patient, resulting in disturbed ability of effective social communication and interaction with the environment. Currently, it is believed that a certain proportion of patients are capable of leading an independent and productive life, while in others the impact of the disease can be very profound, significantly affecting the quality of life (Valkanova et al., 2013; Hofvander et al., 2009) [4].

Some of autistic children (about 10%), despite disorders in the development of the nervous system, can present surprising abilities, usually limited to one domain, which are equal to or outweigh the potential of a normal individual. This is called 'savant syndrome'. It usually manifests as amazing artistic or cognitive abilities (Courchesne et al., 2004) [14].

In terms of causation, environmental factors are interwoven with iatrogenic causes, in particular with vaccination (measles, rubella, mumps), recently cited as one of the most important and somewhat underestimated, although still quite controversial etiological factors [1]. Vitamin D deficiency, which has become the focus of attention as one of the possible causative factors accounting for multiple sclerosis, is also being investigated for its involvement in the development of schizophrenia and autism. Unfortunately, as yet, the research has not provided sufficient number of convincing evidence that vitamin D supplementation may modulate the course of autism and is an important factor in the treatment. This direction of research, however, seems to be very important and could potentially be one of the treatment methods that does not require major financial expenditures. Nevertheless, it requires more attention and further research. Vitamin D is considered a significant factor in the pathophysiology of the nervous system, and can also affect other diseases. It is also combined with the immune response and the immune system, and presented as a neuroprotector or as an agent limiting the inflammatory process [2].

The immune system is vital for the development of the nervous system, regulating the development of neurons, forming synapses and removing apoptotic nerve cells. Dysfunction of the immune system in ASD may be responsible for the inflammatory conditions in the nervous system, the presence of antibodies, increased immune response of T lymphocytes, as well as NK cells and monocytes. The studies on mice in the autism model showed that behaviors can be improved by modulating some elements of the immune system [3].

Infections in pregnancy, the presence of antibodies against fetal nervous system antigens, and family-related autoimmune diseases also seem to contribute to the pathobiological process in autism. Also, some drugs, toxins and elements of the diet are mentioned as having a negative impact on the development of the fetal nervous system, and a possible risk factor for the development of ASD [4].

Review articles also showed that there is a relationship between exposing the fetus to increased sugar levels and the occurrence of autism (Gardner et al. 2009, Xu et al. 2014) [11]. A positive correlation was also demonstrated by the analysis of the impact of maternal gestational diabetes as a risk factor for ASD. The research was conducted

on a large, multiethnic group of children who were born as single fetuses between 28th and 44th weeks of pregnancy with the exposure to gestational diabetes diagnosed before 26th week of pregnancy (Xiang et al 2015) [15].

In the colloquial understanding, autism spectrum disorders are considered to be disease entities from a wide group of neurodevelopmental disorders without a more precisely determined etiology. The disease syndrome usually occurs before the age of 3, although it is most often diagnosed when the child is around 4.5 years old, and the symptoms are most pronounced. Both environmental influences and genetic changes in various proportions are referred to as pathogenic agents. ASD occurs from 4 to 10 times more often in boys. Among many theories trying to explain this phenomenon, one of the more intriguing is the so-called 'extreme male brain theory' [5].

The authors try to show the effect of increased testosterone levels on the brain development during fetal life as the cause of manifestations of the extremely male brain (both in male and female patients). It is an attempt to develop the empathizing-systemizing theory put forward for the first time in 1997, based on the observation of the differences in emotional reactions between males and females, trying to explain why male gender is more susceptible to autism. The main pillar of this assumption is the widespread belief that women have a stronger predisposition to express empathy, while men are more likely to systematize. According to this theory, ASD is the expression of the so-called extreme masculinization of the sick child's brain and the loss or disorder of empathy (both genders) [6, 7, 8].

The theory of chromosome X, based on the assumption that many genes associated with the development of the brain are located in chromosome X, and the aberrations can produce a significant effect. Another theory of chromosome Y based on a similar thesis provides an alternative [9, 10, 11, 12, 13]. Although quite interesting, none of these theories has yet been supported by sufficiently convincing scientific evidence. The attempt to create a comprehensive theory explaining the etiology and incorporating all three above-mentioned factors was not sufficiently proven, either [14, 33].

Autism spectrum diseases are manifested by serious disorders in the field of socialization, communication, and repetitive atypical reflexes and behaviors. Those are symptoms considered as crucial and necessary for harmonious coexistence in today's society. In addition, a significant group (about 75%) of patients exhibit symptoms that seriously hinder their daily functioning, requiring significant social assistance and creating a burden on society [15].

The phenotypically complex syndromic forms of autism are characterized by coexisting clinical conditions such as congenital defects and dysmorphisms, microcephaly, macrocephaly and other changes. Co-existing problems and disturbances in everyday life are very common not only among patients but also families of children with ASD, and can have a significant impact on the functioning of the whole family and the progress of treatment [16]. Parents of children affected by this disease also show an increased incidence of stress and concomitant mental disorders, such as depression and anxiety disorders, which may be related to the child's problems and behaviors [17].

Other behavioral and developmental diseases co-existing with ASD include intellectual disability, intellectual development disorders, symptoms of incoherence or increased physical activity, as well as increased impulsiveness, e.g. attention deficit hyperactivity disorder (ADHD). Dysphoric states are quite common, especially as a manifestation of experienced negative emotions inadequate to situations, which may take the form of aggression in trivial situations, sleep disorders, and disturbed sensory integration [18]. Other co-existing medical conditions include gastro-esophageal reflux, selectivity of foods as well as other neurological diseases, including epilepsy. These diseases can have a significant impact on the treatment and functioning of the family. For these reasons, comprehensive diagnostics of developmental disorders should include very detailed studies of causative relationships and the identification of concomitant diseases [19].

EPIDEMIOLOGICAL DATA

In 2015, Atladottir et al. conducted comparative studies on the frequency of diagnosis of childhood-related psychiatric diseases in several countries (Denmark, Finland, Sweden and Western Australia). The research covered children born in these countries in the period of January 1990 - December 2007 and remaining under observation until December 2011. The patients' records were searches for four disease entities: autism spectrum diseases, hyperkinetic syndrome, Tourette syndrome, and obsessive-compulsive disorder. The researchers

noted a significantly increased incidence of all four types of diseases [20].

The analysis of ASD diagnosis in the last 30 years found a rapid increase in the incidence of this disease. Whether it is the result of a real increase in morbidity or a change in the definition of diagnosis, which would entail artificial overestimation of statistics or other factors, is still the subject of scientific debate [21, 22, 23, 24, 25, 26]. Autism can pose serious diagnostic difficulties, by nature presenting itself rather as a spectrum of conditions than a single disease, especially if the severity of symptoms varies greatly between patients.

Earlier studies in the United States (Blaxil, 2004) show an increase from less than 3 cases per 10,000 children in 1970 to 30 per 10,000 in 1990. In the United Kingdom, there was an increase from less than 10 cases per 10,000 in the 1980s to around 30 per 10,000 in the 90s [27]. In one study, the incidence amounted to as many as 116 cases per 10,000 children [28]. This study was conducted on a small number of patients in South Themes, UK. It also included all cases diagnosed as autism spectrum diseases by a very broad-spectrum definition. When the definition was narrowed, the reported incidence decreased to 25 per 10,000. According to the CDC data, the frequency of autism diagnosis increased by 78% in the United States between 2002 and 2012 indicating a significant social problem and burden for the health care system [28].

The classification and nomenclature were even more complicated when the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) was published. Concerns arose regarding the potential difficulties in monitoring the continuity of the hitherto studies and results, and planning further treatment [29]. According to DSM-V, the definition differs significantly from those provided by the Diagnostic and Statistical Manual of Mental Disorders-IV and DSM-IV-R. Diseases from autistic spectrum were counted as one separate group, which reflected the agreement between researchers. Four previously considered separate disease entities are in fact treated as one disease of various severity of the symptoms [30].

In 2014, Kulage et al. conducted a meta-analysis of 418 studies aiming the assessment of the DSM-V impact on the diagnosis of ASD. The results showed a decrease in the diagnosis of ASD (between 7.3-68.4%) by the DSM-V criteria. The most common reason was the failure to meet all three criteria in the domain of communication and social interaction (deficit in socio-emotional reciprocity, deficit in non-verbal communication behaviors in social interactions, and deficit in development, maintenance and understanding of relationships adequate to the level of development) [30].

In 2016, the CDC ADDM platform (Autism and Developmental Disabilities Monitoring) reported that about 1 in 68 children in the United States were diagnosed with ASD. This number had remained unchanged since 2014, which was the first year when no increase was recorded. If compared to previous years, the rating signaled an increase of around 30% compared to previous reports, i.e. 1 out of 88 children in 2012. In the 1980s, the prevalence of patients with autism in the United States was 1 in 10,000 children, and in the 1990s it was 1 in 2,500, later 1 in 1,000. The comparison over the last 30 years has been very problematic due to continually changing diagnostic criteria.

According to Hansen et al. (2015), the increased incidence of autism is mainly due to changing definition. However, the study was limited to one country only [31]. In addition, changing the definition itself cannot account for such a significant soar, so the search for other etiological factors remains open.

CONLCUSIONS

The classification, diagnosis, and causes of the observed increase in ASD prevalence still cause a lot of controversy. Currently, genetic factors are the mainstream of research interests as they are perceived as one of the key causative factors.

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