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MINI REVIEW ARTICLE

PERINATAL COMPLICATIONS, ENVIRONMENTAL FACTORS AND AUTISM SPECTRUM DISORDERS

PERINATALNE KOMPLIKACIJE, FAKTORI SREDINE I POREMEĆAJI AUTISTIČNOG SPEKTRA

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ABSTRACT

Objectives: Autism spectrum disorders (ASD) are characterized by qualitative impairment of social interactions, impairment of verbal and nonverbal communication, as well as restricted interests and repetitive behavior. ASD represent a group of complex psychiatric disorders, with both genetic and environmental factors implicated in their etiology. Recent neuroanatomical and epidemiological studies point out to prenatal and early postnatal genesis of ASD.

Aim*:* In this review, we present recent studies that explored the effect of environmental, prenatal and perinatal risk factors on development of ASD. Also, we point out those factors that have been proven to have the strongest association with ASD, and emphasize a very complex interaction of individual factors that might eventually lead to manifestation of this group of disorders.

Conclusion: A precise defining of risk factors might provide more insight not only into etiology of ASD, but might also give us a possibility for early recognition and possible prevention of autism spectrum disorders, especially in susceptible individuals. It is also a first step in defining the basis of the gene-environment interaction mechanism, which might enable the development of an individualized therapeutic approach for this group of disorders.

Keywords:
autism spectrum disorders,
autism,
risk factor,
perinatal complications

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SAŽETAK

Uvod: Poremećaji autističnog spektra (engl. *autism spectrum disorders*, ASD) karakterišu kvalitativna oštećenja socijalne interakcije, poremećaj verbalne i neverbalne komunikacije, kao i ograničena interesovanja i repetitivno ponašanje. Ovi poremećaji spadaju u kompleksne psihijatrijske poremećaje, u čijoj etiologiji značajnu ulogu imaju i genetski i faktori spoljne sredine. Skorašnje neuroanatomske i epidemiološke studije ukazuju na prenatalnu i ranu postnatalnu genezu ASD.

Cilj: U ovom preglednom radu predstavljene su skorašnje studije koje su ispitivale uticaj koji prenatalni, perinatalni i faktori spoljne sredine mogu da imaju na razvoj ASD. Ukazano je i na one faktore za koje je u najvećoj meri pokazana povezanost sa ASD, kao i na veoma kompleksnu interakciju individualnih faktora koja može da dovede do manifestacije ove grupe poremećaja.

Zaključak: Precizno definisanje faktora rizika moglo bi da omogući bolji uvid ne samo u etiologiju ASD već i rano prepoznavanje i potencijalnu prevenciju poremećaja autističnog spektra, posebno kod osoba sa predispozicijom za ovaj poremećaj. Ono je, takođe, prvi korak u razumevanju osnove interakcije gena i okoline, što može da omogući razvoj individualizovanog terapijskog pristupa u lečenju ove grupe poremećaja.

Ključne reči:
poremećaji autističnog spektra,
autizam,
faktori rizika,
perinatalne komplikacije

Autism spectrum disorders (ASD) are a group disorders characterized by the following main clinical characteristics: qualitative impairment of social interactions, impairment of verbal and nonverbal communication, as well as restricted interests and repetitive behavior. ASD are also characterized by early onset, slow development of key psychological functions, variation of symptoms with age and a chronic course with different levels of impairment of functioning (1).

According to the 10th International Classification of Disorders (2), ASD, referred as Pervasive developmental disorders include autism, atypical autism, Rett syndrome, childhood disintegrative disorder, Asperger syndrome, hyperactive disorder with mental retardation, other pervasive developmental disorders, and pervasive developmental disorder, unspecified. These disorders differ in the level of symptoms, of intellectual impairment, level of speech, and co-morbidity (3). According to the latest research, the prevalence of autism in children of 8 years of age is 1 in 68 (23.6 in 1000 boys and 5.3 in 1000 girls) (4). The prevalence of ASD is averagely four times higher in boys than in girls, which has been explored in several ways – using biological studies (5), but also exploring sex specific differences in clinical symptoms of ASD (6). Furthermore, recent analyses from 2008 indicate that the prevalence of autism has increased 23% since 2006 (7). Beside the changes made in the diagnostic criteria and registration of ASD, the increase in prevalence of ASD is also supposed to be related to the effect of various environmental risk factors. Understanding the effect of these risk factors, as well as gene-environment interactions, could have important implications for prevention and treatment of these disorders. Besides the fact that it is important to identify the specific risk factors, it is also important to define how these factors lead to the development of the disorder in susceptible persons. That way, the basis of the gene-environment interaction mechanism could be defined, enabling the development of potential biological forms of therapy for this group of disorders (8).

Although the period of the highest sensitivity to environmental risk factors has not been precisely defined for ASD yet, evidence of neuroanatomical and epidemiological studies point out prenatal and early postnatal genesis of ASD (9). Evidence for this claim can be found in the fact that neuronal connections and signaling pathways have been proven to change in ASD, and these are the systems which develop in exactly prenatal and perinatal periods of development (10).

In 1956, few years after the first definition of autistic syndrome, correlation of pregnancy complications and ASD has been studied for the first time (11). If the increase in diagnosis of ASD is an actual increase of incidence of these disorders, it is supposed that this is due to a new risk factor, or an increase of influence of an already existing risk factor (12). There is a variety of prenatal and perinatal risk factors which can increase the risk of ASD development. These factors can be classified as the exposure to environmental factors, and the existence of prenatal and perinatal complications.

Exposure to environmental factors

Environmental risk factors for ASD are defined as those non-genetic factors which can influence the development of the disorder in persons who are genetically predisposed (8). Chemical environmental risk factors are external, and enter the organism via ingestion, inhalation, dermal absorption, injection or via placental transportation (10). Environmental factors linked to development of ASD are the exposure to mercury and led, varicella virus, retinoid acid, use of thalidomide and valproic acid during pregnancy, use of alcohol during pregnancy, or, in general – nutritive factors, taking medication during pregnancy, pesticides and infections (8, 13). So far, the strongest correlation between medication and ASD has been proven for valproates (14, 15, 16). The correlation that has been

proven important in the past years, and is also important in the context of their very frequent use, is the correlation of SSRI use in pregnancy and ASD. Still, this correlation hasn't been confirmed yet. Besides the studies that have found a correlation between the use of SSRI in pregnancy and ASD disorders (17, 18), there are also studies that have found no correlation (19), or studies in which the correlation has become insignificant after controlling for confounding factors (20). The other factors that have been explored for ASD are exposure to tobacco, air pollution, volatile organic substances and metals (10).

Prenatal factors/complications

Prenatal factors can be divided into familial and pregnancy related factors.

1. The familial factors

This group of factors include parental age and parity.

1.1. Maternal age is defined as a risk factor for ASD in a study by Mamidala and authors (2013) (OR=1.80)(21). A cohort study which included 5 million children found that the risk for ASD increases with maternal age, independently of paternal age, which was also found in a study by Durkin et al in 2008 (22, 23). In another cohort study in 2007, it was found that the risk for ASD increases with every 10 years of maternal age (24). On the other hand, in a study done in Israel in 2006, it was found that the risk for ASD didn't increase with maternal age, when controlling for paternal age. The same study showed that the risk for ASD increases 5.75 times in fathers over 40, when comparing to those below 30 years of age, after controlling for year of birth, socioeconomic status and maternal age (25). Similar results were obtained in Iranian population, where again it was proven that ASD risk increases with paternal, but not maternal age (26). In several other studies, it was shown that ASD risk increases with paternal age (22-25, 27-29) while in a study done in 2013, this was not confirmed (21).

The correlation of maternal age and ASD might be explained by the fact that, with age, there are certain changes in biological mechanisms in women, such as hormonal status alterations, epigenetic changes, nucleotide repeats instability, etc. (30). The synergistic effect of all of these factors might influence the fetal brain development and lead to ASD (22, 30).

The theory that explains the results of aforementioned studies, where it has been shown that the correlation of paternal age and ASD is much stronger than the one of maternal age and ASD, has been explained in a recent paper, where it is argued that the development of male and female germ cells is rather different, with spermatozoids undergoing much more cell divisions than oocytes (31). Every time a cell division occurs, the whole genome passes through the replication process, leading to mutations (32). A recent study of the whole genome sequencing including parents and offspring confirmed that about 80% of de novo mutations are paternal in origin, as well as that the number of mutations correlates with paternal age (33).

1.2. Parity and inter-pregnancy interval

Increased risk for ASD has been found in first-borns (34-37) the fourth and after the fourth child (35). On the other hand, no significant difference was found between first-borns and non-first-borns in a study by Duan et al, done in 2014 (29). Another study found that women who had an inter-pregnancy interval of less than 18 months, as well as those that were nulliparous, are at an increased risk for having a child with ASD. A short inter-pregnancy interval can be related to the theory of "reproductive stoppage"- a tendency that having an affected child limits further pregnancies. The families with a short inter-pregnancy interval might not be aware of their child's status (ASD) when they plan another pregnancy (34).

2. Maternal state/pregnancy complications

It has been shown that the risk for ASD is increased my maternal hypertension (OR=1.8) (21) and pre-pregnancy maternal diabetes (38). The increase of risk for ASD was shown for maternal respiratory infections as well (OR=1.8) (21). This finding can be explained by immunological maternal response, which leads to cytokine release, and their sequent passing through trans placental barrier and modulation of neuronal function, survival, apoptosis, as well as expression of transmitters in a developing brain (39). Cytokines also influence neuronal proliferation and differentiation, which is also related to ASD (40).

The increased risk has also been confirmed for preeclampsia and pregnancy bleeding, before the 20th gestational week (38, 41). In a systematic review done in 2012, the factors identified as main pregnancy-related ASD risk factors were pregnancy bleeding and preeclampsia (28). When it comes to use of medication during pregnancy, a recent study has shown increased ASD risk with the use of so-called prescription drugs. It was shown for lithium, antihypertensive therapy, antidepressants and anticoagulant therapy (34).

Smoking during pregnancy has not been explored in many studies. A study done in 2006 showed no correlation of pregnancy smoking and ASD (42), while another study proved it to be a risk factor (43). Also, a study that examined this potential risk factor in a Chinese population, didn't have a number of smoking mothers large enough to reach the conclusion, but it showed that "second hand" smoking can also increase the risk for ASD (44). This finding was later confirmed in another study (29).

Perinatal and neonatal factors and complications

The perinatal factors, in the aspect of ASD etiology, are related to the period of the delivery itself. These factors include pre and post maturity, delivery-related factors (pelvic presentation, prolonged delivery, and Caesarean section), meconium aspiration and fetal distress.

When exploring the effect of prematurity, researches have used different number of gestational weeks. A prematurity of less than 26 weeks has been proven to be a significant risk factor in a recent study (45). Other studies have used later gestational weeks as a prematurity criterion – prematurity of less than 37 weeks doubles and triples the risk for ASD (OR=2.11; OR=3.32) (21, 29, 46). In a recent study that compared perinatal characteristics in low-risk and high-risk children (in terms of ASD), it was shown that the average number of gestational weeks at the time of delivery was significantly lower in the high-risk group, with average differences being three gestational weeks (47).

Other factors have been determined as ASD risk factors – asphyxia at birth (21, 29), fetal distress, defined as intrauterine hypoxia and neonatal asphyxia (48), and respiratory distress syndrome – OR=2.13 and 1.48 (34, 49).

Several studies confirmed that birth weight of less than 2500gr is a significant risk factor for ASD (38, 48, 50), while it was not confirmed in a more recent study (21).

The first minute Apgar score of less than 7 has been defined as a risk factor in two studies (34,38), less than 6 in one study (46), while in two studies, low Apgar score was not proven to be a ASD risk factors (46, 51).

Intracranial hemorrhage during delivery has also been an ASD risk factor in studies – it increases the risk for ASD two times (34). The total risk for ASD in case of intracranial hemorrhage, cerebral edema and convulsion was tripled in a study done in 2009 (49).

Neonatal jaundice/hyperbilirubinaemia has been proven to be a risk factor for ASD in a large number of studies, increasing the risk for approximately three times (21, 44, 46, 51, 52). On the other hand, one study found no correlation between neonatal jaundice and the increased risk for ASD (53). Neonatal jaundice is the result of accumulated bilirubin (mostly conjugated), physiological or pathological, as a result of increased fetal hemolysis and liver immaturity. A visible jaundice can be seen in 60% of term born neonates, and in 80% of preterm neonates (54). In higher concentration, bilirubin is considered to lead to damage of central nervous system, or even encephalopathy (44).

A large review study done in 2012 included all the studies up to 2011 that had explored perinatal risk factors for ASD. According to this review, neonatal risk factors for ASD are low birth weight, head circumference, low Apgar score, markers of hypoxia, respiratory distress syndrome, assisted ventilation, hyperbilirubinaemia, encephalopathy, congenital anomalies, and neonatal/congenital infections (28).

As it is shown in this review, different studies used different criteria for specific risk factors, and the results are mostly inconsistent. This has been confirmed in a meta-analysis done in 2011 (55), which had determined a large heterogeneity of results, leading to conclusion that more replication of results is needed, using methodologically more rigorous studies, for most of the perinatal and neonatal variables. According to this study, a lot of peri and neonatal risk factors reached inconsistent results. It is important to point out that any observed correlation of perinatal complications with ASD might actually represent consequences of former prenatal complications, meaning that it is difficult to undoubtedly confirm an isolated effect of a single factor (56). The inconsistency of results can be explained by the fact that not a single, but a combination of several risk factors might lead to increased risk for ASD.

Conclusion

Studies have shown a significant increase of ASD prevalence in recent decades. Although the increase can partially be explained by the changes in the diagnostic approach, a significant part of this increase still requires clarification. A variety of environmental factors might explain these findings – the increase in air pollution, use of medication during pregnancy, increase in parental age, but also the fact that, due to its development, modern medicine manages to surpass prenatal and perinatal complications which have, until recently, been incompatible with life.

A clear and precise defining of risk factors provides more insight not only into etiology of ASD, but also provides us with a large possibility for early recognition and possible prevention of autism spectrum disorders, especially in susceptible individuals. Also, early recognition provides the possibility of early interventions which have been proved effective in persons with ASD, leading to better outcomes for this group of disorders.

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