NOWAK, Gabriela, SZTYBÓR, Mateusz, MOMOT, Karol, KAPICA, Marcin, ŻMIJEWSKA, Aleksandra, KRZYŻANOWSKA, Maria, MALESZEWSKA, Monika, PIĄTKIEWICZ, Julia, WOJTAS, Mikołaj and GŁOGOWSKA, Karen. Screened potential risk factors for autism and autistic behaviour in children. Literature review. Journal of Education, Health and Sport. 2024;55:231-247. eISSN 2391-8306. https://dx.doi.org/10.12775/JEHS.2024.55.015
https://apcz.umk.pl/JEHS/article/view/47964
https://zenodo.org/records/10591172

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 10.01.2024. Revised: 27.01.2024. Accepted: 28.01.2024. Published: 30.01.2024.

Screened potential risk factors for autism and autistic behaviour in children. Literature review

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Abstract

Introduction and purpose: This publication is a review of research on potential risk factors for the development of autism and autistic behaviour in children. The purpose of this review is to spread knowledge and awareness of autism syndrome disorder.

Brief description of the state of knowledge: Autism syndrome disorder is a neurological and developmental brain disorder. It is characterized by problems with social relationships and communication as well as narrow and repetitive behaviours and interests. The causes of autism spectrum disorder are still not fully understood and pose a challenge to modern medicine. Numerous studies find causes in fetal life and the course of pregnancy, genetic conditions and mutations, environmental risk factors or vaccination. Many theories about the causes of autism require more extensive and thorough research, for which some beliefs have been overturned, such as the search for links between autism spectrum disorder and childhood vaccination. At this point, the role of genetic mutations in the occurrence of autism in children can be confirmed with certainty. The reasons for the occurrence of these mutations are not fully known. Causes are particularly looked for in fetal life and prenatal factors. One theory relates to the activation of the mother's immune system, her production of cytokine and pro-inflammatory factors that affect the development of the fetal nervous system.

Material and methods: The literature review was conducted using English medical databases and focused on articles in the English language that cover various factors causing ASD.

Results and conclusions: In our review, we aim to present the risk factors that can most significantly influence the development of ASD. These factors include genetics, prenatal diet, smoking during pregnancy, maternal intake of antidepressants, infections during pregnancy, other pregnancy and maternal factors, parental age, various paternal risk factors, lack of breastfeeding, and environmental factors. Some factors need more research for a comprehensive understanding, while others, like breastfeeding and non-smoking during pregnancy, are well-studied and require promotion to reduce the risk of the disorder.

Keywords: ASD, autism behaviour, pregnancy, paternal factors, environmental factors

Main Text

Introduction and purpose of the study:

Autism syndrome disorder (ASD) is a set of heterogeneous neurodevelopmental conditions. It is characterized by early-onset difficulties in social communication and unusually restricted, repetitive behaviour and interests. According to WHO it's estimated that 1 in 100 has autism. Due to the growing global awareness of ASD, numerous educational projects have been developed for parents, children, doctors and therapists to face this challenging disorder. Causes of autism are variation of multiple factors such as genetics, environmental, prenatal and maternal. Treatment is multifaceted and it includes early intervention, educational and school-based therapies, behavioural therapy, nutritional therapy. This publication is a review of more than a dozen studies for factors that increase the frequency of ASD.

Material and methods

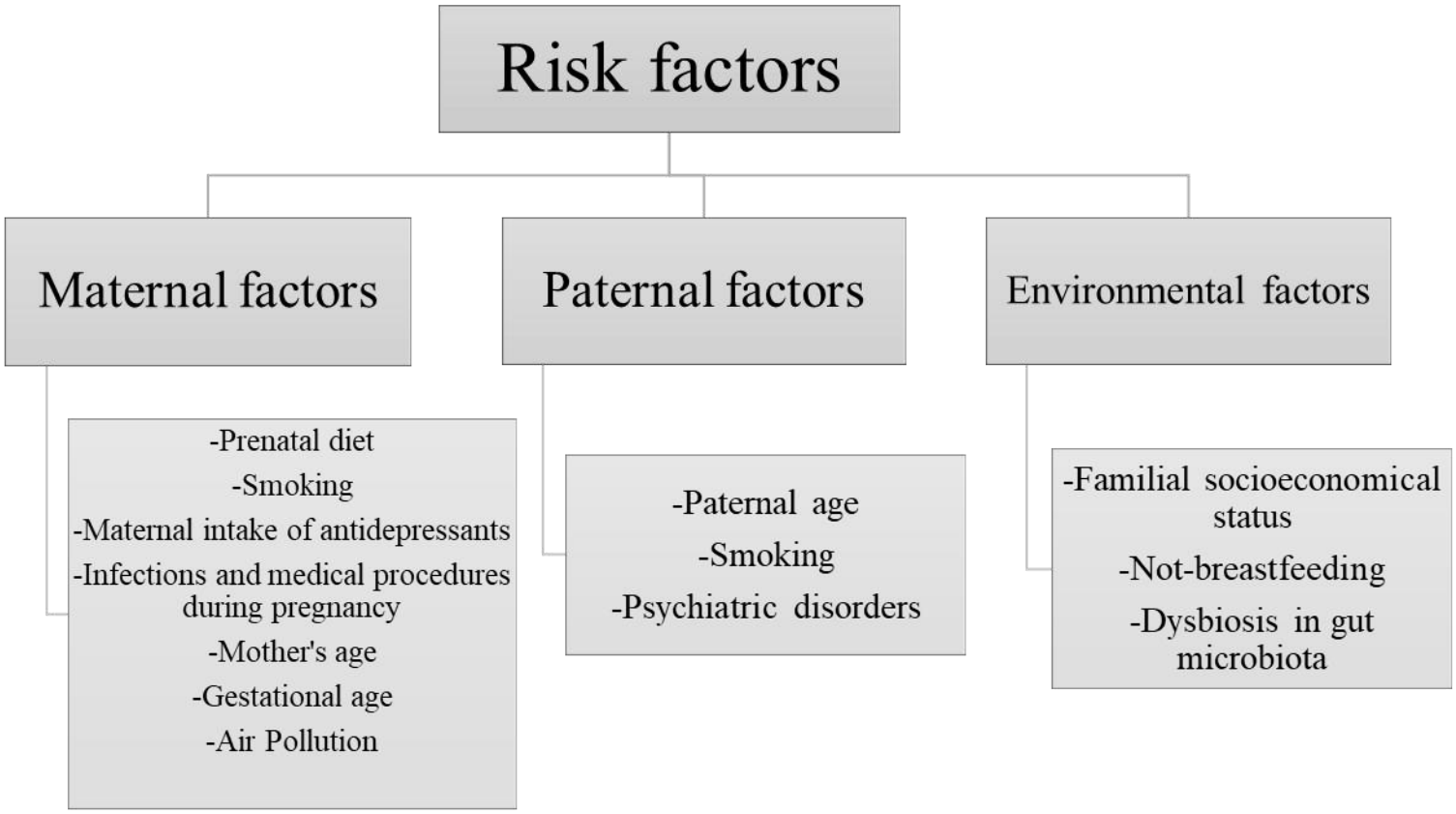
We conducted our literature review using English databases such as PubMed, Google Scholar, and PubMed Central. In our search for articles, we used keywords such as ASD, autism, behavior, pregnancy, and environmental factors. The articles

we utilized were published between 2018 and 2023, and we selected those most relevant to our summary.

Results:

We have divided the risk factors with the greatest impact on the development of ASD into three groups (Diagram 1) and will describe them in more detail below.

Diagram 1- Risk factors for autism and autistic behaviour in children



Genetic risk factors

The earliest mention of the genetic etiology of ASD date back to the study on twins in the 1970s. The impact of genetics has been confirmed by the high concordance of autism in monozygotic twins compared to dizygotic twins. The heritability of ASD is estimated to be 45-65%. Genetic heritability combined with environmental or epigenetic factors, plays a fundamental role in the development of ASD. Whole-genome studies have led to the discovery of six single nucleotide polymorphisms (SNPs) in the CDH10 and CDH9 genes on chromosome 5, which encode cadherins.

However, the individual variant effects are modest. In addition to SNPs, changes in copy number (CNVs) have a significant impact. ASD patients exhibit 3-5 times more de novo CNVs than unaffected individuals. Over 800 genes have been identified in association with autism, with a particular emphasis on genes encoding proteins involved in chromatin remodeling, cell proliferation, and synaptic function. The involvement of genetic defects in various ion channels is well-documented in ASD development. Mutations in the CACNA1C gene, encoding a calcium channel, lead to Timothy syndrome with an autistic phenotype. Genetic changes in sodium channel genes, such as SCN1A, SCN2A, SCN3A, SCN7A, and SCN8A, have also been linked to ASD [14].

Several genetic syndromes and chromosomal disorders including tuberous sclerosis, fragile X, and Rett syndromes, count less than 10% of all ASD cases. Mitochondrial dysfunctions are present in 10-20% of ASD patients, often involving small mitochondrial DNA deletions/duplications. Inborn errors of metabolism may contribute significantly to ASD causation, with enzyme deficiencies leading to the accumulation of harmful substances, exerting toxic effects on the developing brain [34].

Pregnancy and maternal factors

1.Prenatal diet

An important factor that can affect the development of the fetal nervous system is the mother's diet. Two studies conducted in the United States have analyzed the relationship between maternal dietary patterns and the incidence of ASD in offspring. Although the analysis of these studies did not show a clear correlation future and additional research is needed.

Includes research on higher maternal intake of pro-inflammatory foods and unhealthy diet and the incidence of ASD in children. Studies of the effect of maternal diet on increased risk of ASD are particularly promising [8].

Diet is the most significant area of maternal exposure to pesticides. The correlation between maternal exposure to dietary pesticides during pregnancy and the incidence of autism-related traits in children was examined. The study found no correlation between a mother's pesticide intake during pregnancy and autism-

related traits in her offspring. At the same time, it was noted prenatal high intake of vegetables and fruits reduced the chance of child autism-related traits [9].

Deficiency of certain components in the mother's diet, especially vitamins, can have serious consequences for the child's health. Recently, the relationship between maternal vitamin D levels during pregnancy and the incidence of autism in the child has become an object of interest. A study analyzing 7689 child births in the United Kingdom between 1991 and 1992 found no relationship between maternal vitamin D levels and the incidence of autism in the child [1].

2.Smoking

Smoking cigarettes during pregnancy can cause miscarriages, premature births, and fetal growth disorders. However smoking during pregnancy can contribute to the occurrence of autism has been examined. Analyses have shown that there is insufficient evidence to link nicotinism in the mother during pregnancy and the occurrence of autism in the child [2,3].

However, an analysis of other studies shows that there may be a link between nicotinism and increased risk of ASD in a child. Given these conflicting reports, additional future studies are required [13].

3.Drugs

The effect of substances taken by the mother on the fetus is of great importance.

Maternal intake of antidepressants has been associated with occurrence of various neurodevelopmental disordes such as ASD. A possible link between prenatal exposure to antidepressants and the onset of ASD in the child was analyzed. A meta-analysis of 14 studies found no such association [4]. Also, another retrospective, multi-cohort study found no such association [5]. In contrast, another restrospective analysis of 123,824 pregnancies in the US found an association between a mother's intake of antidepressants and the onset of ASD in her child. Therefore, it is clearly visible, that more research is needed to take a definite position [11]

4.Infections

It is known that infections during pregnancy with specific pathogens crossing the placental barrier can cause abnormalities in fetal development. Infectious agents such as rubella, cytomegalovirus or herpes viruses can affect the

neurodevelopment of fetus, causing brain calcification, microcephaly and other disorders. The effect of infection during pregnancy on the appearance of ASD in the offspring was analyzed. Activation of the mother's immune system during infection may be a potential factor in the development of ASD in the offspring. Although the results of the study are not clear, and require further additional research to fully understand the role of cytokines and inflammatory processes in mothers and the development of ASD in their children [6].

It appears that Toxoplasma gondii infection in the mother may play a role in the onset of autism in the child. In a study of 36 mothers and their children from Saudi Arabia, results indicate a possible link between infection and increased risk of ASD in the child. Infection of the mother leads to infection of the fetus and consequently the formation of mutations in fetal DNA that increase oxidative stress production causing neurodegenerative diseases such as ASD [10].

5.Medical procedures

An analysis of the course of more than 120,000 pregnancies in the US showed an elevated risk of ASD in the child if the mother had surgical procedures, and radiology exposure or hospital visits [11].

6.Mother’s age

The age of the mothers also turns out to be not insignificant. It is associated with autistic-like traits. This relationship is best illustrated by the U-shaped curve. This means that extremely young as well as older mothers are more likely to develop ASD in their offspring. The reason for this result is not known. It is possible that the reason for this result for younger and older mothers is the same, but it could also be a multiple mechanism [7].

7.Gestational age

A very important factor in child development is prematurity and the complications that result from it. Noteworthy is a study analyzing the birth of children in the northern European countries of Sweden, Finland and Norway. Based on it, there is a link between gestational age and the risk of ASD. Risk increased weekly as the date of delivery diverged from 40 weeks, both pre- and post-term, independently of sex and size of baby [12].

8.Air pollution

Research from Taiwan also indicates that exposure in all 3 trimesters to air pollutants such as CO and NO2 influences an increased risk of ASD in the child [14]. Other studies seem to support these conclusions [15]. The theory explains this relationship by activation of the mother's immune system, which affects fetal neurodevelopment. However, the authors themselves point out the need for more studies to thoroughly analyze the process of activation of the maternal immune system and the mechanism of how the produced factors and cytokines affect the fetus.

Paternal Risk Factors

1.Paternal age

In research, numerous factors on the father's side are identified as having a significant impact on the occurrence of ASD. One of the largest single risk factors for autism was an older or unknown father [27][31]. The significant association between ASD development and fathers over 40 years old is prominently demonstrated. Children whose fathers were over 40 had a 1.91-fold higher likelihood of developing this disorder compared to the control group [18]. Similar conclusions can be drawn from another study, indicating an increased risk of ASD in offspring when the father is over 40 at the time of the child's birth [19].

2. Paternal smoking

The influence of paternal smoking on the birth of a child with ASD is noticeable. Prenatal smoking by fathers increases the likelihood of having offspring with ASD. The cessation of smoking by fathers can reduce the risk of having a child with ASD by 11-14% [20]. Both active and passive smoking during pregnancy were significantly more prevalent among parents. A striking difference is observed in the percentage of fathers from the ASD group who smoked compared to the control group (76.9% vs. 16.3%). This pattern is also evident among fathers who were passive smokers in the ASD group (67.3%) compared to the control group (14.7%) [35].

3. Paternal Psychiatric Disorders

The prevalence of parental schizophrenic and psychotic disorders, mood disorders, anxiety disorders, and personality disorders is higher among ASD cases than in the control group[28] [32]. However, it should be noted that the impact of mental disorders in mothers on the risk of ASD in children is bigger than in the case of mental disorders in fathers [28].

The closer the relationship with an individual affected by a mental illness, the bigger the likelihood of ASD in the child. For fathers, depression, like in mothers occurring in any time window, may increase the risk of having a child with ASD. Attention should be paid to a very large genetic study that found 20 loci common to major depression and ASD [30].

4. Paternal use of antidepressant

The use of antidepressants by fathers during the conception period is considered safe. It is not associated with an increased risk of autism, premature birth, congenital defects, or intellectual impairment [29].

Environmental factors

1.Familial socioeconomic status

Families with a child with ASD showed lower socioeconomic status, meaning these families had lower levels of education and a smaller family income [24]. Low socio-economic status leads to increased parental stress, resulting in less involvement in the education of children with ASD. Parents may feel frustration and stress, also associated with growing costs arising from the need to allocate significant amounts of money for rehabilitation, which can hinder their fulfillment of parental duties and, consequently, result in less engagement in the education of their children with ASD [21]. Results regarding the impact of parental education on the risk of ASD are inconclusive and may require further research [32].

2.Breastfeeding

Not breastfeeding is a risk factor for ASD. The risk of ASD in non-breastfed children has an odds ratio of 1.81 (95% confidence interval, 1.35–2.27; I2=0%). This suggests

the need to pay attention to the role of breastfeeding in children and to consider this relationship as a positive aspect of breastfeeding [23]. Breastfeeding reduces the risk of ASD by 58%, while exclusive breastfeeding reduces this risk by 76%. Breastfeeding for 12-24 months is associated with the most significant decrease in the risk of ASD [22].

Although a study of 2-5-year-old children with ASD in the USA did not show a significant association between breastfeeding and the occurrence of ASD, the result of 76.6% of breastfed children, including 10.1% exclusively breastfed, suggests the need for appropriate actions. All practices and campaigns promoting breastfeeding among parents of children with ASD or parents at high risk of having a child with ASD, are essential [24]. Prolonging the breastfeeding period is associated with much better cognitive development and a reduction in autistic traits in children [18].

Despite the protective role of breast milk, it is important to remember that early insufficient nutrition/hydration can lead to long-term consequences such as autism or specific learning difficulties. Therefore, to avoid the consequences mentioned above, it is necessary to feed hungry neonates with the most appropriate available supplemental milk [33].

3.Vaccination

Even a minimal increase in the risk of autism after MMR vaccination is highly unlikely [27]. Due to the increased prevalence of ASD, there have been many voices in society linking ASD to vaccinations. When ASD occurs in children, parents may feel anger and seek reasons for dangerous behavior during pregnancy, genetics, or other risk factors. However, there is no association between the development of ASD in children and their vaccination. After the publication of Wakefield's study in 1998 linking the MMR vaccine to autism, parents experienced many concerns. Therefore, attention should be paid to promoting and implementing campaigns encouraging vaccination and advocating for it [25].

An interesting aspect of this matter may be the views of mothers, the majority of whom pointed to childhood vaccination as the cause of autism in their children. One-third of mothers in this study indicated that, in their opinion, their child's autism resulted from a combination of two or more factors such as specific

conditions of the newborn or the mother in the moment of delivery, genetics, and vaccines [26].

4. Gut microbiota

One of the more popular theories is the role of the gut microbiota in the development of autism. Dysbiosis causes increased toxic metabolic production. This triggers an increase in the production of pro-inflammatory cytokines such as IL-6, IL-10, TNF-alpha. The formation of generalized inflammation negatively affects brain neurodevelopment and leads to ASD [16]. This creates new opportunities for the development of diagnostic methods AND therapies for children with ASD [17].

Conclusion:

In this review, we sought to summarize the factors that can most significantly influence the development of ASD. We aimed to encompass factors that have been intensively researched and documented in recent literature. These factors include genetics, maternal influences (such as maternal age, diet, medications taken, infections during pregnancy, gestational age, and others), paternal risk factors, and environmental factors, with a particular focus on non-breastfeeding. It is crucial to pay attention to these factors that can have the greatest impact on the development of this condition, as well as parental behaviors that can reduce the risk of its occurrence. This highlights the importance of raising awareness among future mothers and fathers during pregnancy, as well as before and after pregnancy. Healthy behaviors such as a nutritious maternal diet and avoiding harmful substances, including smoking, should be emphasized. Additionally, attention should be given to the medications taken by the mother. Early detection of genetic disorders and proper attention to child feeding are also essential. All of these practices enable prompt issue diagnosis and the implementation of appropriate treatment.

Disclosures

Author’s contribution

Conceptualization:Gabriela Nowak, Mateusz Sztybór; Methodology: Marcin Kapica, Karol Momot; Formal analysisAleksandra Żmijewska, Julia Piątkiewicz; Investigation: : Mikołaj Wojtas, Karen Głogowska; Writing - rough preparation: Maria Krzyżanowska, Monika Maleszewska; Writing - review and editing: Mateusz Sztybór, Gabriela Nowak; Supervision: Gabriela Nowak, Mateusz Sztybór.

All authors have read and agreed with the published version of the manuscript.

Funding Statement- This Research received no external funding.

Institutional Review Board Statement-Not applicable.

Informed Consent Statement- Not applicable.

Data Availability Statement- Not applicable.

Conflicts of Interests- The authors declare no conflict of interest.

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