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Autism – risk factors and treatment

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Abstract
Introduction: Autism spectrum disorder (ASD) is a group of pervasive neurodevelopmental disorders that are characterized by persistent moderate to severe impairment in social skills and communication but also repetitive or stereotyped behaviours and interests. Many factors have been suggested to cause autism. However, its aetiology is still not fully understood. There are many kinds of treatments: behavioural treatment, pharmacological approach and alternative medicine (CAM) therapies.

The aim of the study: The purpose of this systemic review was to collect and analyse available data about aetiology and treatment of ASD.

Material and method: Standard criteria were used to review the literature data. The search of articles in the PubMed database was carried out using the following keywords: autism spectrum disorder, aetiology, treatment.

Description of the state of knowledge: The study that is one of the biggest population-based twin studies of autism shows that heritability of autism is around 55%. Literature reports that approximately 10% children with autism or ASD have other chromosomal or genetic disorder and the most common is Fragile X and it is the most common cause of autism. Several environmental risk factors were thought to be the cause of autism. Nevertheless, only some of them might have an influence on developing ASD. There are many forms of behavioural treatment, but only two drugs were approved for ASD symptoms treatment. CAM offers many different therapies but their efficiency is not strong enough.

Summary: The aetiology of ASD remains unclear. Reports of different factors being cause of developing ASD are not consistent. When it comes to treatment, early diagnosis and intervention are very important and can result in better onset of the disorder. ASD is subject of many researches but still even more is needed to answer the questions of aetiology and successful treatment of ASD.

Keywords: autism spectrum disorder, aetiology, treatment

1. Introduction

Autism spectrum disorder (ASD) is a group of pervasive neurodevelopmental disorders that are characterized by persistent moderate to severe impairment in social skills and communication but also repetitive or stereotyped behaviours and interests [1]. Additionally, there are other symptoms such as anxiety, aggression, hyperactivity, gastrointestinal symptoms and insomnia [2].The prevalence of ASD estimates on global scale that 1 in 160 children have ASD with increased occurrences in boys [3]. Before determining autism as a developmental psychiatric/neurological disorder, it was stigmatized [4]. Many factors have been suggested to cause autism. However, its aetiology is still not fully understood. There is a reasonably well-defined etiology of autism in up to 10 percent of autism cases while most cases are idiopathic [5]. Early behavioural intervention and use of approved drug are recommended [3]. Many behavioural and educational treatments for the core symptoms of ASD were established as the standard, although they require time to show improvement and not every patient benefits from them [2].

2. Autism risk factors

2.1 Genetic risk factors

The recurrence risk of pervasive developmental disorder in siblings of children with autism is 2% to 8% and several studies suggest that this phenomenon is more gene-dependent rather than environment-related [6,7,8,9]. One study on children born in Sweden shows that heritability of ASD and autistic disorder is approximately 50% [10]. Another study shows that monozygotic twins have higher concordance rates than dizygotic twins for ASD [9]. Similar study which is one of the biggest population-based twin studies of autism shows that heritability of autism is around 55% [11]. Literature reports that approximately 10% children with autism or ASD have other chromosomal or genetic disorder and the most common is Fragile X and it is the most common cause of autism [12]. Oxytocin is important neuropeptide hormone. Studies found that genetic variation in the oxytocin-gene may be associated with

phenotypic features of ASD. One European study shows association between oxytocine-gene rs6084258 and several endophenotypes of ASD [13]. Chromosome impairments can also be the cause of autism. A pathogenic deletion or duplication in chromosome 15q13.3 have been implicated as a locus for autism [14]. There are many other genetic factors which could be the cause or risk factor of autism or ASD, such as SH3 and multiple ankyrin repeat domains 3 mutations, contactin-associated protein-like 2 reactive antibody, tryptophan hydroxylase 2 gene, sporadic mutations and other genetic interactions [15].

2.2 Environmental risk factors

There are several environmental risk factors of autism or ASD, some of them are confirmed in the literature, while others are unconfirmed and replicated by e.g. anti-vaccine environments. We can distinguish factors such as pollution, valproate exposure, vaccination, advanced parental age, pregnancy-related complications and conditions, medication use during pregnancy, maternal smoking and nutritional factors [15]. The study named CHARGE shows that autism cases were more common among people living near the highway than those living far from the highway [16]. The results of these study suggest that traffic-related air pollution could be related to autism. However, there are several studies that do not confirm this findings. Rossignol et al evaluated two groups of studies based on direct or indirect assessment of exposure. The most consistent finding was for an association between environmental mercury exposure and ASD [17]. De Palma et al compared hair concentration of heavy metals (mercury, copper, cadmium, selenium, and chromium) between patients with ASD and controls. Their study found no evidence for an association between hair metal concentration of these heavy metals and ASD [18]. How chemicals affect the development of neurodevelopmental diseases can be based on their neurotoxicity or alteration in DNA methylation [15]. There are evidences that valproate exposure during pregnancy, can cause ASD in children. The usage of this medicine for the treatment of epilepsy in pregnant women should be cautious and used only in necessary situations [19]. Kobayashi et al reviewed eight studies (five case-control and three cohort) of using selective serotonin reuptake inhibitor (SSRI) during pregnancy and found a 50% increase in risk of ASD of mothers who took selective serotonin reuptake inhibitors. However, when the authors conducted a sensitivity analysis comparing the SSRI-exposed group with the non-SSRI-exposed group in a mother with mental illness, they found no significant increase in the risk of ASD in the offspring [20,21]. Literature reports that advanced parental and maternal age could be a risk factor of ASD. Wu et al reviewed 27 studies on association between advanced parental and maternal age and ASD. They found that every 10-year increase in maternal and paternal age increases the risk of ASD in the offspring by 18 and 21% respectively [22]. To perinatal risk factor of autism we can also include gestational diabetes. Gestational diabetes could adversely affect the fetal growth, and increase the rates of pregnancy complications and it also had impact on motor development, and lead to the learning difficulties and attention deficit per activity disorder [23,24,25]. It could be caused by increased fetal oxidative stress or epigenetic changes in the expression of genes [26]. Rosen et al did meta-analysis of 15 studies of association between smoking during pregnancy and ASD in the offspring. They found evidence that there was no association between maternal smoking and risk of ASD in the offspring [27]. However, the study conducted by Zhang et al, suggests that maternal second-hand smoking during pregnancy is associated with an increased risk of autism in the offspring, because of fetal hypoxia and influenced brain development, due to exposure to polycyclic aromatic hydrocarbons, and metals [28]. A lot of studies try to find association between nutrition and ASD. Several studies show lower zinc levels in children with ASD [29]. Wang et al analysed 11 studies of the association between vitamin D and ASD. They found lower levels 25-hydroxy vitamin D in patients with ASD than those in controls [30]. There are several reports about association between folic acid deficiency and ASD [31,32]. In

1998 Wakefield et al Publisher a paper in Lancet that confirmed positive correlation between vaccination and autism [33]. This study was later retracted because of scientific and ethical dishonesty. Taylor et al conduced a meta-analysis of studies that investigated the association between childhood vaccines and ASD. They found no correlation between vaccination and ASD [34]. However, many people still believe that vaccination could be a cause of ASD.

3. Treatment of autism

There are different types of autism treatment. We can distinguish behavioural treatment, pharmacological approach but also complementary and alternative medicine (CAM) therapies. Autism is being identified earlier and earlier. Thus, there is a need for early intervention [35]. The aim of early detection of ASD is to prevent or alleviate the full onset of the disorder [36]. However, it is still not known which type of treatment or combination of those will be the most beneficial and for which child characteristics [35]. Core symptoms are the main focus of treatment [37]. In order to be effective, behavioural and developmental treatments for ASD need to be addressed to the behavioural, social, and communication deficits [38]. The target of treatment of core symptoms should be socialization, communication and behaviour [37]. Fluency and flexibility of expressive language are one of the main factors that differs "high-functioning" and "low functioning" autism in school age or adolescence. Early intervention aimed at communicative acts is beneficial for children with autism [39]. And those can be divided into three major categories: didactic which draws on behaviourist theory and uses behavioural technologies, naturalistic which include behaviourist basis in more natural environments and developmental/pragmatic that underline multiple aspects of communications [39]. Applied behaviour analysis (ABA) includes highly intensive and structured trials of repeatedly presented stimuli coupled with positive reinforcement in order to induce target behaviours. More advanced ABA are more individualized and comprehensive but also aim to follow more natural and normal developmental sequence [40]. However, this kind of treatment is challenging due to the time needed to see improvement and the amount of motivation to work but also due to its cost [41]. Another treatment is pivotal response treatment (PRT) which is a naturalistic behavioural approach focused on core pivotal areas. Its goal is to teach children to respond to learning opportunities and social interactions [42]. Moreover, the study of two approaches mentioned above showed that PRT was more effective at improving social communication skills for children with ASD compared to ABA [43]. Children with autism need intensive and well organised educational service [44]. Because of the targets of therapeutic interventions which are social and communications deficits it is hard to measure the improvement taking into consideration changing targets of young developing child [45]. Pharmacotherapy does not treat core symptoms but they targets attention-deficit/hyperactivity disorder (ADHD), sleep disorders, affective difficulties, interfering repetitive activity, but also irritability, aggression, and self-injurious behaviour [37,46]. US Food and Drug Administration (FDA) approved two drugs, which are risperidone and aripiprazole, for ASD symptoms treatment [47]. Risperidone works by blocking the brain's receptors for dopamine and serotonin and is thought to be safe and effective for the short-term treatment for children with ASD. Risperidone showed improvement of aggression and self-injurious behaviour [48]. However, risperidone have side effects like weight gain which is the most common but also somnolence [49]. Aripiprazole is an atypical antipsychotic, a partial agonist of serotonin 5-HT1A and dopamine D2 receptors, also a 5-HT2A receptor antagonist [50]. Aripiprazole was shown to be effective and safe, but also well tolerated for treating irritability in autism [50,51]. At present, there is no effective drug for the core social and communication impairment. Although, most promising drugs are the glutamatergic drugs and oxytocin but still more trials of those potentially effective drugs are needed [52]. It is not surprising, that parents are seeking for an alternative treatment in order to help their children with ASD. Complementary alternative medicine is quite popular

although there are not many evidences supporting those methods. The most often used forms of CAM are modified/special diets, vitamins/minerale and food supplements [53]. Pathophysiological mechanisms potentially related to ASD are immune dysregulation and inflammation, environmental toxicant exposures, oxidative stress and mitochondrial dysfunction [54]. CAM therapies aim to improve abnormalities in these areas. It has been suggested that exposure of fetuses to maternal inflammation increases the likelihood of developing ASD [55]. Exposures to environmental toxicants can damage cells and was implicated in some psychiatric disorders, among others ASD [54]. Oxidative stress is defined as 'an imbalance in pro-oxidants and antioxidants' and disruption of redox circuity association [56]. Free radicals cause damage to cellular tissue [54]. Mitochondrial dysfunction and defects in oxidative metabolism are linked to the pathogenesis of many chronic illnesses which are although not classified as mitochondrial diseases [57]. It is suggested that oxidative stress, mitochondrial dysfunction and inflammation/immune dysfunction in the brain of ASD individuals are important in the pathological mechanisms in ASD [58]. N-acetylcysteine (NAC) is an orally bioavailable prodrug of cysteine [59]. The study of NAC effect on core social impairment in youth with ASD showed that although the treatment was well tolerated, it had no significant impact on the core social impairment [60]. Vitamin B12 is a vital cofactor in the antioxidant system that takes part in the regeneration of methionine from homocysteine [61]. Vitamin B_{12} levels in human frontal cortex decrease with age. Moreover, it was suggested that deficits of methylcobalamin in autistic and schizophrenic subjects and then impaired methylation may be a critical pathological component of these brain disorders [62]. Another form of CAM are dietary interventions. The gluten-free/casein-free (GFCF) diet is the most popular [53]. Experimental studies of the use of those diets suggest improvement of symptoms and development for at least a proportion of people with ASD [63]. Other studies suggest to identify the subtypes of ASD individuals who might benefit from these diet [64]. The ketogenic diet is thought to be beneficial for treating epilepsy [65]. The study of ketogenic diet showed a positive influence on BTBR mouse. Juvenile BTBR mice were fed standard or ketogenic diet for three weeks. The study showed improvement in BTBR mice in the three core deficits of ASD: reduced sociability, deficits of communication and increased repetitive behaviour [66]. However, there is not enough reports of improvements after treatment with ketogenic diet to validate it as a treatment [67]. Camel milk is the closest to a human mother's milk and in some places in the world it was traditionally used for treating autism. Camel milk is thought to have positive effects on autism symptoms and lowers effects of oxidative stress [68]. Another study also suggests a potentially important role of camel milk in decreasing oxidative stress and treating ASD. That may be due to high level of antioxidant vitamins C, A, and E in camel milk and being very rich in antioxidant minerals magnesium and zinc [69]. Chelation therapy is another form of CAM treatment in which chemicals are administered in order to bind heavy metals. However, this treatment is based on a not proven theory of autism being caused by heavy metal poisoning like mercury [70]. The risk associated with this therapy is bigger than its potential benefits so it is not recommended for patients with ASD [53].

4. Summary

The aetiology of ASD remains unclear. Factors like vaccination or maternal smoking seems to have no impact on developing ASD. Another ones like using selective serotonin reuptake inhibitor (SSRI) during pregnancy need more studies. However, there are evidences that valproate exposure during pregnancy, can cause ASD in children. This is why usage of any medications by pregnant women should be very careful. When it comes to treatment, early diagnosis and intervention are very important and can result in better onset of the disorder. Behavioural treatment and pharmacological approach seems to be a standard treatment. However, many parents try CAM therapies although they might not have evidences of their

beneficial effects. ASD is subject of many researches but still even more is needed to answer the questions of aetiology and successful treatment of ASD.

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