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The role of genetic factors and pre – and perinatal influences in the etiology of autism spectrum disorders – indications for genetic referral

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Summary

Autism spectrum disorders (ASD) are caused by disruptions in early stages of central nervous system development and are usually diagnosed in first years of life. Despite common features such as impairment of socio-communicative development and stereotypical behaviours, ASD are characterised by heterogeneous course and clinical picture. The most important aetiological factors comprise genetic and environmental influences acting at prenatal, perinatal and neonatal period. The role of rare variants with large effect i.e. copy number variants in genes regulating synapse formation and intrasynaptic connections is emphasised. Common variants with small effect may also be involved, i.e. polymorphisms in genes encoding prosocial peptides system – oxytocin and vasopressin. The environmental factors may include harmful effects acting during pregnancy and labour, however their specificity until now is not confirmed, and in some of them a primary genetic origin cannot be excluded. In several instances, especially with comorbid disorders – intellectual disability, epilepsy and dysmorphias – a detailed molecular diagnostics is warranted, which currently may elucidate the genetic background of disorder in about 20% of cases.

Key words: genetics, autism spectrum disorders, aetiopathogenesis

Introduction

Autism spectrum disorders (ASD) were placed as a new diagnostic category in the chapter "Neurodevelopmental disorders" within fifth version of the American Psychiatric Association classification (DSM-5). Two core ASD symptoms, i.e. disturbances of social communication and stereotypical behaviors might be present since early months of life; however the diagnosis is usually made in preschool age. The causes of early onset of symptoms are searched in the disturbances of brain development, which can be caused by genetic and pre – and early postnatal environmental factors.

Genetics

Genetic factors play an important role in the etiology of autism spectrum disorders (ASD). Risk of illness is significantly increased in first-degree relatives (siblings, children) and identical twins show a high concordance rate of the disorder [1]. Over 3,000 genes and many thousands of gene variants have been identified so far, from rare mutations to common polymorphisms, which may be associated with ASD [2]. The role of genetic factors in the risk of the disease, referred to as heritability, for ASD may be the highest among all psychiatric disorders – approx. 0.8–0.9 [1], although some recent analyzes indicate values of the 0.4–0.7 range [3]. Genetic variability responsible for the disease can be successfully identified in approximately 20–30% of cases. Those are mostly rare genetic defects: single gene mutations, chromosomal aberrations and micro-aberrations. They fit into the concept of the, so called, common disease–rare variant (CD-RV) suggesting that the presence of a single, rare or very rare defect (mutation) of significant effect, or accumulation of such defects decides on development of symptoms [4, 5]. Another hypothesis, common in current studies on the genetic architecture of ASD, is the common disease–common variant (CD-CV)

one, according to which occurrence of symptoms is a result of overlapping of variants common in the population, but separately having a minor effect in pathogenesis of the disease (small-effect changes). Many of rare and common genetic variants observed in ASD are also present in intellectual disability, attention deficit hyperactivity disorder (ADHD), epilepsy and schizophrenia. On one hand that may suggest existence of a some kind of continuum of neurodevelopmental disorders dependent on genetic and environmental factors, and on the other hand, it may indicate a significant role of complex interactions between numerous genetic factors [6].

In less than 5% of cases chromosomal aberrations visible in examination of karyotype are responsible for the phenotype of autism – most commonly they are duplications in the 15q11-q13 region. Deletions in chromosome 15 of respectively maternal and fraternal origin lead to Angelman and Prader-Willi Syndrome. In approximately 5–10% of cases copy number variants (CNV), micro-deletions and micro-duplications of DNA fragments invisible in standard karyotype examination are responsible for the disease [7]. The whole genome analysis for the copy number variants in ASD indicates the following: in autistic people CNV are several times more frequent than in the control group, hereditary variants and formed *de novo* in the same genes may account for ASD, many CNV increase the risk of various neurodevelopmental disorders, including intellectual disability, ADHD and schizophrenia. Micro-deletions and micro-duplications may occur in single genes, but also in loci containing several or several dozens of genes, as it is in case of the 16p11.2 region, containing approx. 30 genes [8]. CNV in genes located on the chromosome X, such as *PTCHD1/PTCHD1AS2* and *NLGN3* may explain a higher prevalence of ASD in males. Also the number of known mutations in single genes, which may lead to the development of the disease, is still growing. The most common case of that kind is the fragile X syndrome, caused by a mutation in the *FMR1* gene (approximately 2% of autism cases). ASD-associated CNV discovered so far are present in genes coding proteins participating in intercellular transmission processes, ubiquitin-mediated intercellular catabolism, neuronal migration, axon direction and synapse formation, especially of glutaminergic neurons [9, 10]. On the other hand, sequencing of the whole exon indicates that in a significant number of cases, *de novo* mutations may lead to the development of the disease [11]. All identified genes that increase the risk of ASD are also associated with an increased risk of intellectual disability [12].

Linkage studies in autism brought no unequivocal results. A linkage signal was observed for a large number of chromosomes, but none of subsequent studies confirmed the initial observation at the nominal value of $p = 0.01$, postulated as the condition of a confirmed linkage [13]. Linkage regions are described below, in the paragraph regarding association studies. In case of small effect genetic factors, studies focusing on differences in frequency of particular allele (case-control studies) and analysis of differences in allele transmission (family studies or parent-child pair studies) may have more statistical power compared to studies of linkage and the whole genome analyses. In association analysis, genetic variants that may potentially participate in

etiology of a disorder are selected, based on their localization in regions previously demonstrated in linkage studies or postulated pathogenic mechanism. Among the most important genes with a suggested role in the pathogenesis of autism are several ones selected due to their chromosomal localization. In the region 2q31-32, previously reported as autism-linked [14], there is the *SLC25A12* gene (for the mitochondrial aspartate/glutamate carrier protein), associated with ASD in several studies [15, 16]. However, not all studies confirmed existence of that association [17]. Initial reports on the *RELN* gene for the extracellular matrix protein reelin, participating in shaping of cerebral cortex cytoarchitecture, and mapped in the 7q21-22 region (previously mentioned in linkage studies), confirmed existence of an association with autism, although further studies gave negative results [18, 19]. The variability within another gene mapped at the long arm of the chromosome 7, in the region linked with autism (7q35) – *CNTNP-2* (the gene coding a protein belonging to the family of neurexins, participating in construction of synapses) demonstrated an association with ASD in two studies [20]. A potential participation in the risk of the disease, considering their neurobiological effect, may be postulated for genes of the social peptide system (oxytocin/vasopressin), genes of the glutamate/GABA system and genes of the serotoninergic system. It was observed that the 20q13 region, containing gens coding oxytocin/vasopressin, demonstrates a linkage with autism [21], although no significant association with polymorphisms within genes encoding social function-affecting neuropeptides has been reported yet [22]. However, several studies demonstrated association of ASD with variability within the oxytocin receptor gene [23, 24]. Similarly, some studies indicate an association between the risk of autism and variability within the vasopressin receptor gene [25, 26]. In 30–40% of cases autism co-exists with epilepsy, and that may indicate the relative advantage of excitatory over inhibitory mechanisms in the cerebral cortex. At the neuropharmacological level that could be mirrored with a dominance of the glutamatergic over the GABA-ergic system. Several studies reported an association of autism with markers within the gene for the GABRB3 receptor [27], although also in that case results were not unequivocal [28]. Holt et al. [29] observed an association of autism with the polymorphism within the type 2 glutamate ionotropic receptor gene, *GRIK2* (GluR6) in the European population. In case of studies on two Asian populations, contradictory results were obtained [30]. There are also reports indicating a common pathogenesis of Tourette Syndrome and ASD [31], and of mood disorder symptoms and ASD [32]. It is suggested that disturbances in the development of dopamine – and GABA-ergic neuronal networks may be associated with co-existence of affective symptoms and ASD. Increased blood serotonin level is a biochemical marker of autism reported before 1970s [33]. Several studies indicated the importance of a short variant of the serotonin transporter gene in risk of ASD [34, 35]. However, the meta-analysis failed to confirm that association [36]. Three largest genome-wide association studies (GWAS) published so far gave somehow divergent results [21, 37, 38]. Moreover, Devlin et al. [39] demonstrated that analysis of pooled results of those three studies

gave a result that was not statistically significant. That may mean that the analysis of study groups of several thousand individuals will be necessary to find some common variants increasing the risk of autism using GWAS-type studies.

Prenatal, perinatal and environmental factors

An incomplete concordance of the disorder in monozygotic twins suggests an important role of environmental factors [40–43]. Pre – and perinatal factors are among them. Some authors treat those factors as: an independent noxious agent, being a cause of ASD, an effect of common pathogenic mechanism, leading both to gestational and perinatal complications, and to development of autism later in life, or as an expression of a different intrauterine development of a fetus that may lead to gestational, perinatal and neonatal complications, and to development of ASD symptoms in later life [41, 43].

The first report on complications during pregnancy and their association with the risk of autism was published in 1956 [44]. Three currently the largest meta-analyses [41–43] included papers published before 2007 [42] and some methodologically correct papers published later (before 2010) focusing on significance of individual factors for development of ASD [41, 43]. Among events demonstrating the higher repeatability and hazard ratio (HR) there are numerous factors acting on various stages of a child's development.

Authors emphasized that factors occurring already before conception were significant. One of them is age of parents. It was found that the risk of ASD increased by 7% with each 5 year period over the maternal age of 30, and by 3.6% in case of father's age. It was also observed that the maternal age in the range of 30–34 caused a 27% increase in risk of the disease compared to the population of mothers younger than 30, and the age over 40 caused the increase by 106%. Some authors claimed that only the age of father is important, and that each 10 years over the age of 40 causes a 2–3-fold increase of chance of ASD development [42]. Order of births was also mentioned among important factors. The oldest child of two elderly parents is at 3-fold increased risk of ASD [45]. Another study indicated that children born as first – in case of two siblings – and born as third or subsequent – in case of large families – more often demonstrate symptoms of autism [42]. The risk of ASD in case of affected older siblings is 2–8%, if one child is affected, and as high as 20%, if two or more children are affected [46, 47]. Other factors that play an important role before conception of a child are family autoimmune factors [48, 49] and maternal metabolic factors (e.g. obesity, diabetes, hypertension) [50].

Many authors reported an important, even crucial in some cases, effect of factors occurring during pregnancy on increased risk of ASD [40, 43, 51–54]. They are: intrauterine exposure to high level of androgens measured in amniotic fluid, drugs, including valproate, metamizole, thalidomide (ASD risk increase by 20–46%) and some other psychotropic agents, especially SSRIs. Other studies point to bleeding throughout the pregnancy (ASD risk increase by 81%), multiple pregnancy, intrau-

terine infections (TORCH, bacterial, other), serological conflict (in the AB0 and Rh system), maternal hypothyroidism (ASD risk increase by 25–40%). Gestational diabetes, particularly type II, is one of the best documented factors. Its existence in mother causes even 2-fold increase of autism prevalence – probably associated with hormonal disorders, metabolic disorders and oxidative stress. Also arterial hypertension during pregnancy seems important, along with pre-eclampsia and eclampsia, severe anemia, smoking during the pregnancy [55, 56], and also various factors causing dopamine level increase in pregnant women [57], including stress, especially associated with tension within the family with a simultaneous lack of emotional support, as well as sleep deprivation.

Delivery is another stage when events may occur that significantly increase the risk of ASD [41, 42, 58]. Among those factors there are: delivery before the 37th week of pregnancy, pelvic position, emergency cesarean section, umbilical cord-related complications, low (< 2,500 g) and very low birth weight (< 1,500 g), intrauterine hypotrophy (low body weight in relation to the gestational age), low Apgar score at 1 minute, and especially at 5 minutes, and necessary RKO and oxygen therapy of a neonate.

Also neonatal factors may influence development of symptoms of autism [40, 41, 53, 59]. The most commonly mentioned ones are: flaccidity and hyporeactivity of a child, or spasticity and hyperreactivity of a neonate, respiratory disorders, specific motor pattern, intraventricular bleeding, jaundice or hyperbilirubinemia and congenital defects.

Protective environmental factors are also studied. Schmidt et al. suggest that consumption of folic acid during the 1st month of pregnancy may be one of them, particularly in case of mothers with the *MTHFR 677* C >T gene variant [55]. A similar effect could be offered by consumption of vitamins and supplements for three months before the conception and during the first trimester of pregnancy. However, the protective effect was only confirmed in case of genetically-conditioned metabolic disorders (mother variant – *MTHFR* 677TT, *CBS*rs 234715 GT+TT; child variant – *COMT* 472AA) [55, 60].

Indications for a genetic consultation

From the clinical point of view, confirmation of presence of additional, so called, phenotypic variables (markers or endophenotype) is a very important element of diagnostic evaluation, increasing the chance of determination of genotypic causes of ASD. They are: disorders of physical development, accompanying mental disorders, neurological problems, aspects of the disease natural history and family history data [61]. The first group involves in particular: developmental defects, including defects of the CNS, dysmorphia traits in body structure and micro – or macrocephaly. Coexistence of intellectual disability or other neuropsychiatric disorders may be an exceptionally valuable clue. Epilepsy occurs in approximately 25% of population of autistic children, and abnormal EEG is found in 50% of patients. Age of symptoms onset is

equally important (the earlier the age, the higher the risk of presence of a rare *de novo* mutation). Family history data should consider the presence of ASD phenotype and of other neuropsychiatric disorders (especially of intellectual disability, epilepsy and schizophrenia, but also of bipolar affective disorder or alcohol dependence).

Based on a detailed clinical evaluation considering presence of the above discussed diagnostic markers, a patient should be pre-qualified to the group of autism not accompanied by other clinical symptoms (essential autism), or the autism+ group (complex autism) with co-existing other, previously mentioned, phenotypic features [62]. That procedure, following the application of appropriate diagnostic techniques, leads to increased probability of making a diagnosis of a genetic background of ASD in patients in the autism+ group by 20–30%. As indicated by study results, that does not eliminate a chance for identification of a pathogenic variant in the population of patients in the autism group [63].

The task of a specialist in clinical genetics is to determine a genetic cause of the disease of autistic spectrum using a detailed clinical evaluation and available diagnostic techniques, to formulate some practical recommendations regarding the management and prevention of symptoms and complications of the disease, and to provide a reliable genetic counseling regarding repeated occurrence of autism in the family.

Indications for consultation by a specialist in clinical genetics should concern ASD cases accompanied by: 1) intellectual disability, delayed psychomotor development, or cases when intellectual disability cannot be excluded; 2) developmental defect(s) or body structure anomalies; 3) macrocephaly > +3 SD or microcephaly > – 3 SD; 4) structural dysmorphia; 5) developmental regression; 6) family history of ASD or neuropsychiatric diseases in first-grade relatives (siblings, parents); 7) abnormal result of a genetic test. Those indications for special consultations are justified by results of clinical trials. According to them, the more complex and the more severe clinical presentation of ASD is, the higher is the risk of identification of a pathogenic change (mutation or chromosomal aberration) [64].

Conclusions

Autism spectrum disorders constitute a new category in the DSM-5 classification. Despite the fact that ASDs show a significant heritability, only genes with a large effect, but occurring in rare cases have been successfully identified so far. Whereas studies of genetic factors which may contribute to ASD pathogenesis on the basis of neurobiological hypotheses, have given no unequivocal results. It is suspected that larger study samples will be necessary to achieve that goal, as well as selection of more homogenous populations of ASD patients. The role of environmental factors also seems indisputable. Among them, the above discussed gestational, perinatal and neonatal factors constitute probably an expression of an altered development of a child, who subsequently will be diagnosed with autism. Further studies are necessary, aimed at determination of phenotypes of ASD patients in whom individual etiological factors

played a special role in development of the disease. The diagnosis of a genetic cause of ASD is reached in approximately 20–30% of patients. Therefore, in some cases there are indications for referral to clinical genetics specialist.

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