AUTISM SPECTRUM DISORDER - NEW RESEARCH CONCEPTS OF ETIOLOGY

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Autism spectrum disorders are a group of disorders with increasing prevalence. The main clinical manifestation of this group of disorders are persistent deficits in social communication and interaction, and restricted, repetitive patterns of behavior, interests and activities. The etiology of this group of disorders is still unknown, although a large number of studies is oriented toward discovering it's causes. The studies are multidimensional and explore different aspects of autism - genetic factors, brain morphology, somatic disorders in children with autism, as well as the influence of pre and perinatal factors on the risk of autism spectrum disorders. All of these studies might lead to the finding of an early and practical biomarker which might make early detection possible. Until then, it is very important to point out to the early clinical signs of autism, which might improve the overall outcome of this disorder. In this paper, we summarize the clinical manifestations of autism spectrum disorders, the findings of studies covering different aspects of etiology, and also emphasize the early warning signs of autism, as well as the important role pediatricians might have in early detection of this group of developmental disorders.

Descriptors: AUTISM SPECTRUM, ETIOLOGY, CHILDREN

Abbreviations:
ASD - Autism spectrum disorders; DSM V - Diagnostic and Statistical Manuel of Mental Disorders; RDoC - Research Domain Criteria; ADHD - Attention-deficit/hyperactivity disorder

Autism spectrum disorders (ASD) is a group of developmental disorders with increasing prevalence worldwide, and yet it has unclear etiology. The Center for Disease Control and Prevention released data on the prevalence of autism in the United States in 2014. This surveillance study identified 1 in 68 children (1 in 42 boys and 1 in 189 girls) as having ASD (1). A new report shows that a three-fold increase in autism among special education students between 2000 and 2010 is partly offset by a decrease in diagnoses for intellectual disability (2).

According to the Diagnostic and Statistical Manuel of Mental Disorders, Fifth edition (DSMV classification), edited by American Psychiatric Association, two main diagnostic criteria of ASD are: persistent deficits in social communication and social interaction across multiple contexts

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Rad preuzet iz:
Paediatr Croat. 2016; 60 (Supl 1): 113-118.

and restricted, repetitive patterns of behavior, interests, or activities - stereotyped or repetitive motor movements, use of objects, or speech (3). Symptoms must be present in the early developmental period, and cause clinically significant impairment in social, occupational, or other important areas of current functioning.

Children diagnosed with ASD have impairment in social approach, normal back-and-forth conversation, reduced sharing of interests, emotions, or affect; they present with failure to initiate or respond to social interactions; they also have deficits in nonverbal communicative behaviors used for social interaction (poorly integrated verbal and nonverbal communication; abnormalities in eye contact and body language; deficits in understanding and use of gestures; lack of facial expressions and nonverbal communication), deficits in developing, maintaining, and understanding relationships (difficulties adjusting behavior to suit various social contexts, in sharing imaginative play or in making friends, absence of interest in peers) (3).

Repetitive and restricted patterns of behavior, interests, or activities can be manifested through stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, speech with echolalia, idiosyncratic phrases). Children with ASD insist on sameness and routines, manifest ritualized patterns or verbal/nonverbal behavior - for example they might show extreme distress at small changes and transitions, rigid thinking patterns, they need to take the same route or eat the same food every day. They might have highly fixated interests, abnormal in intensity or the object of attention - e.g, they might show strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest, hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement). In order to make the diagnosis of an ASD, these disturbances should not be better explained by intellectual disability (intellectual developmental disorder) or global developmental delay (3).

Scientist and clinicians around the globe believe that this disorder might one day be easily and early detected by pediatricians, enabling them to refer infants for early treatment, and leading to better long-term outcomes.

New approach in psychiatry is the approach of Research Domain Criteria (RdoC). The goal of RdoC is to use research to define dimensions defined by neurobiology and behavioral measures, which could possibly cut through current diagnostic categories. This means that the new direction is using neuroimaging, genetic and cognitive science to create future diagnostic schemes (4).

New findings are aimed towards the discovery of an early, clinically practical, and accurate biomarker that would be applicable for the early risk-of-autism detection and referral (5). The findings of a common set of dysregulated pathways raises the possibility that, despite etiological heterogeneity, autism may result from disruption of common developmental pathways in a large percentage of individuals (6). Genetic and non-genetic factors underlying autism must affect multiple regions, tissue types.

“When does autism start?” is one of the most profound questions we face in our field. At present, autism can’t be reliably diagnosed until about 2 years of age. However, parents often notice symptoms before then. In fact, analysis of videotapes of children’s first-birthday parties shows that signs of autism are already present at

that age for many children, even in the cases where parents don't become concerned until months or years later.

However, it is possible that autism starts even earlier; in most medical conditions, the underlying processes are triggered before their signs and symptoms become obvious. A similar chain of events occurs in autism. We know that toxic exposures during pregnancy and complications associated with delivery can disrupt brain processes before birth and shortly afterwards (7). Mutations in the genes associated with autism can affect the brain development and functioning, starting well before birth. Even though the outward symptoms of autism may not be apparent immediately after birth, the underlying brain differences are accumulating. Sometimes the brain can compensate to make up for the disrupted processes. Eventually though, if the disruption was sufficiently severe, the compensatory processes are no longer enough, and symptoms emerge. This may likewise explain many cases of autistic regression, in which a young child seems to be developing normally, only to lose abilities, or regress, into autism. Perhaps the initial disruption in brain development continued worsening. Or perhaps the compensatory processes couldn't keep up.

Genetics of autism - new research

Autism is considered to be largely a genetic disorder, so finding the genes involved in autism is a logical first step to understanding the complex biology of autism (5). The discovery of autism risk genes and risk regions serves as a foundation for understanding the neurobiology of autism (8, 9). By considering when, where, and how these genes interact, we can focus on the developmental time period, brain region, and cell type that is disrupted in autism.

The results of the largest-ever genetic study of neurodevelopmental and psychiatric disorders revealed strong commonalities between autism and attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, depression and schizophrenia (10). The shared genes included two that balance calcium levels in brain cells, suggesting a common direction for the development of new treatments (11).

Using a systems-biology approach, Dr. Courchesne's team aimed to find a genomic signature from leukocytes that classified with good accuracy two independent cohorts of infants and toddlers with autism spectrum disorder (ASD) (12, 13). They chose to focus on boys to reduce genomic heterogeneity that would accompany a mixed-sex design. Despite the clinical and genetic heterogeneity of autism, a blood-based screen for risk for autism in the general pediatric population may be feasible since it could accurately identify a substantial percentage of autism individuals at early ages; the biosignature utilized the expression patterns from a large number of genes, which indicated the underlying genetic and non-genetic complexity of the disorder. More than 2,700 unique genes have been identified, differentially expressed between the ASD and control populations, with top enrichment in apoptosis, immune/inflammation response and translation networks (12-14). The classification analysis, which used four modules that contained 762 unique genes, provided 83% accuracy for classifying infants and toddlers in the training set and 75% classification accuracy in the independent test set (15). This kind of study is a great first step, but needs to be pursued more along one of the two ways - either to demonstrate that blood samples can be used to help making the diagnosis of autism, or to e go more deeply and conclusively into mechanisms that may be reflected in the cells of the immune system

Autismspeaks is the largest nonprofit organization in the world to support

autism awareness and research, with the mission to alter the future for all who struggle with ASD. This historic collaboration between Autism Speaks and Google is queueing up 10,000 anonymous autism genomes and making the data freely available for research anywhere, anytime. They have started the MSSNG Project; MSSNG is the search for the missing "10K Autism Genomes Program" which demonstrated the usefulness of the whole genome sequencing for providing unprecedented guidance for the diagnosis and personalized treatment for autism and its associated medical conditions. By studying identical twins who differ in autism diagnosis or symptom severity, recent studies have found important evidence showing how environmental influences may contribute to - or protect against - autism (16). Studies reported several discoveries that linked autism to disruptions in very long genes and the enzymes that control them. The researchers have launched a search for chemicals that prevent these important enzymes (topoisomerases) from performing their role (17). Their discovery may also help explain why autism risk is higher among the children of older parents.

In 2013, two research teams separately reported studies that help determine specific periods in brain development in which genetic mutations can converge into increased risk for autism (18). Their research uncovered surprising commonalities - showing, for example, that many autism-linked genes affect key areas in the same small handful of brain pathways. These findings suggest important new targets for future treatments (18, 19).

Researchers linked a specific gene mutation to a newly identified subtype of autism. In one study with more than six thousand individuals with ASD, the researchers found 15 of them who had a mutation in the CHD8 gene; all of them looked similar, with broad foreheads and wide-set eyes; they have a history of gastrointestinal problems (severe constipation) and disturbed sleep. Experts hailed the finding as a crucial step toward using genomic testing to develop individualized treatments for autism spectrum disorder (20).

It has been shown that children with a genetic deletion previously linked to autism and other neurodevelopmental disorders manifest significant delays in processing sound and language (21). A deletion of a region on chromosome 16 (16p11.2) was linked to a "stunningly high" auditory processing delay known as the M100 response latency (22). This study shows an important connection between genes and neurophysiology, and it may also help to bridge a largely unexplored gap between genetics and behavior (23).

The largest genetic study of autism spectrum disorder (ASD) to date has identified 65 genes that contribute to autism, including 28 for which there is "very high confidence" that they play a role in the risk of developing ASD, a multicenter US research team reports (11). Twenty-seven of these genes are new discoveries, first author Stephan Sanders, PhD, of the University of California, San Francisco, told Medscape Medical News. The study also confirms that there are six larger regions of the genome that are prone to de novo copy number variants (dnCNVs) that contribute to autism risk. The study also hints that small deletion dnCNVs often have a single critical gene (11).

Eye tracking as a biomarker

Researchers have used eye tracking measurements to discover a subtle but consistent decline in eye contact that begins around 2 months of age in babies who develop autism (24). If confirmed, this finding would be the earliest biomarker of autism. It may also represent an opportunity for very early interventions that

could improve the course of brain development, learning and social engagement. It has been shown that babies who begin showing decreased interest in facial expressions at 8 months go on to develop more-severe autism symptoms by age 3. The authors expressed hope that this is an early warning signal and an important window of opportunity for early intervention that improves outcome. Another "Baby Sibs" study found that even earlier differences in social attention - this time at 6 months - point out to high risk for autism (25). The researchers called for the development and testing of very early interventions that engage at-risk babies in enjoyable activities that involve shared attention.

Nutritional factors

In 2013, the results of a large study showed that autism rates are lower among the children of women who take folic acid supplements in the weeks before and after conception. The findings suggest a safe and practical step women can take to reduce autism risk. However, the benefit may turn out to be restricted to women with propensities to low folic acid levels (26).

Researchers using a well-known mouse model of autism found that a probiotic known to relieve gut inflammation also improved social behavior while reducing repetitive behaviors and signs of anxiety. The study added support to the idea that intestinal inflammation can worsen or even cause autism symptoms in humans, and opened the door to clinical trials that will administer the probiotic to children with autism and GI symptoms (27).

In a small placebo-controlled trial, sulforaphane supplements eased autism symptoms in nearly half of 29 participants affected by autism. Experts called the results "promising" but cautioned that larger studies were needed to determine effectiveness and safety (28).

Gastrointestinal symptoms

The results of a large study on a diverse group of children with autism confirmed that they experience high rates of gastrointestinal symptoms. The study went further to associate GI distress with more-severe autism symptoms including social withdrawal and irritability. These findings encourage physicians to look for and treat GI symptoms in children with autism. The first meta-analysis of all peer-reviewed research on autism and gastrointestinal conditions showed that children with autism have four times the rate of GI problems as do other children. At the forefront of this research, further research will need to investigate gut-brain connection in autism (29).

Brain morphology and ASD

Researchers analyzing donated postmortem tissue from children affected by autism found that their brains had a significantly increased density of connections between brain cells (30). These excess synapses appeared to be the consequence of slowing of the normal pruning process, which occurs during brain development. The investigators then used a mouse model of autism to show that they could restore normal synaptic pruning and reduce autism-like behaviors with an experimental medication. They called for further research that might advance to a clinical trial involving people with autism (30).

In a review of published studies, Princeton researchers said they found strong evidence that injury to the cerebellum during pregnancy or birth may be the leading nongenetic cause of autism (31). During brain development, it plays a crucial role in directing cross wiring to other brain regions.

Magnetic resonance imaging (MRI) shows sex differences in corpus callosum neuroanatomy in preschoolers with autism spectrum disorder (ASD) (32). The study adds to a growing body of evidence that there are differences between boys and girls with autism, and these differences may affect how boys and girls are diagnosed with autism, as well as potentially the types of treatments or interventions that boys and girls with autism receive (33).

Altered connectivity in the developing brain may underlie neuropsychiatric disorders and motor impairment associated with preterm birth (34). One study shows that babies born prematurely have weaker structural and functional connections between brain regions linked to attention, communication, and emotional processing; this might help explain their increased risk for disorders, such as attention-deficit/hyperactivity disorder (ADHD) and ASD (34).

The other study suggests that motor impairments associated with preterm birth may result from altered brain connectivity detectable before birth. The brain's structural and functional architecture is exquisitely sensitive to conditions before birth and how alterations to brain circuitry can set the scene for future neurologic impairment long before it arises (35).

Vaccines and ASD

A meta-analysis of ten studies involving more than 1.2 million children affirmed that vaccines don't cause autism. The analysis found that immunization with the measles-mumps-rubella (MMR) vaccine was associated with a slight decrease in risk. Also, a recent study showed that MMR vaccine was not associated with increased risk for autism, even among children at high risk for developing an autistic spectrum disorder (36).

Intrauterine and perinatal factors

Fetal exposure to preeclampsia, and in particular, severe disease, may raise the risk for ASD and developmental delay, a large population-based study suggests. Results from the Northern California-based Childhood Autism Risks from Genetics and the Environment (CHARGE) study show that exposure to preeclampsia in utero was associated with a greater-than-twofold increased risk for ASD and a greater-than-fivefold increased risk for developmental delay, compared with no exposure. Preeclampsia is more common in women who are obese or who have diabetes or chronic hypertension (37).

Older maternal age, being first born, high maternal education, low household income, history of comorbidity, preeclampsia/eclampsia, early delivery, and being male were significantly associated with increased risk for ASD (7). The risk of having a child with ASD was not significantly greater for mothers who had preexisting diabetes or for the overall group of mothers with gestational diabetes compared with the mothers without diabetes, after adjustment for relevant confounders (38).

In a large observational study, pregnant women with gestational diabetes that was diagnosed up to week 26 of the pregnancy had a greater risk of having a child with autism spectrum disorder (ASD) than pregnant women without, independent of other confounders. However, women with gestational diabetes that was diagnosed after week 26 and those with known prepregnancy type 2 diabetes had the same risk of having a child with ASD as women without diabetes (39).

When it comes to prematurity, the studies have used different number of gestational weeks. Prematurity of less than 26 gestational weeks has been proven

to be a significant risk factor for autism spectrum disorders (OR=6.7), while prematurity of less than 37 weeks doubles the risk for this group of disorders (OR=2.11) (7, 40). The increased risk for development of autism spectrum disorders was also proven for asphyxia at birth, as well as low birth weight, low Apgar score, respiratory distress syndrome, hyperbilirubinaemia, encephalopaty at birth, and neonatal/congenital infections (40, 41).

Parental age

Initially, in epidemiologic studies, it was shown that paternal age had an effect on autism risk. This was later verified in biological studies. Mechanism for the effect of paternal age on the risk for ASD could be explained through de novo mutations, when new sperms are created in aging fathers. Paternal age was the strongest risk factor, and maternal age was set aside, but now it is shown that there is an effect from both, independently of each other. Findings from the largest-ever study of parental age and autism risk revealed a complex relationship between parental age and autism risk. The researchers discovered that for both mothers and fathers, the risk for autism in their children increases with age. Both relatively advanced age and relatively young age of mothers has been associated with an increased autism risk, as well as a combined effect from both parents (42). These findings suggest that there may be several mechanisms of influence of the paternal and maternal age, independently. DNA methylation in paternal sperm may contribute to the risk of children's developing autism, a finding that sheds new light on the etiology of this complex disorder (43).

Another question that often comes up is whether the link between parental age and autism risk is greater for the mother or for the father. The current results suggest that the risks are comparable for the sexes. When it comes to mothers having the same age as the father, it seems like the risk is very similar, so a large part of the risk difference may come from the fact that fathers can reproduce at older ages compared to the mothers. Moreover, the risk is even greater when both parents are older and when either the mother or the father is at least 10 years younger than the other parent. These results suggest that multiple mechanisms are contributing to the association between parental age and ASD risk (42).

Children conceived with assisted reproductive technology (ART) are twice as likely to receive a diagnosis of autism compared with their counterparts who are conceived naturally, new research shows (44). They found that this increased risk was largely due to complications of pregnancy and birth, especially when such pregnancies were associated with multiple births. The risk of ART with respect to autism appears to be largely modifiable by restricting the procedure to single-embryo transfer. Knowing that one can largely reduce the risk of autism from an ART conception by restricting the procedure to single-egg transfer is important for women, who can then make better informed decisions (44).

Investigators found almost 200 regions of methylated DNA in the fathers of children at increased risk of developing autism that were significantly associated with performance on a scale assessing autism spectrum disorder (ASD) symptoms at 12 months (43).

Conclusion

Autism is a complex developmental disorder largely influenced by genetic factors, but the development of the disorder itself is also influenced by a large number of parental, intrauterine and perinatal factors, which might ''trigger'' the disorder in a genetically predisposed infant. By

taking all of these facts into account, the role of pediatricians, and especially neonatologists might be very important, in terms of early detection of these disorders. The lack of eye gaze, or even minimal signs of slower psychomotor development in a child who is at risk, could be valuable signs for early detection and early intervention.

A solution for better understanding of the cause of ASD is a global autism public health initiative. Enhancing awareness and understanding of autism, building capacity for research and service excellence and improving the quality of life for individuals with ASD and their families by disseminating best practices is essential for the future facing with increasing problem. We need to collaborate and learn from global partnerships and learn from one another.

NOVČANA POTPORA/*FUNDING*
Nema/*None*

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Sažetak

POREMEĆAJI AUTISTIČNOG SPEKTRA - NOVA ISTRAŽIVANJA ETIOLOŠKIH KONCEPATA

M. Pejović-Milovančević

Poremećaji autističnog spektra su skupina poremećaja s rastućom prevalencijom. Glavna klinička značajka ove skupine poremećaja je postojanje deficita socijalne komunikacije i interakcije, uz ograničene repetitivne obrasce ponašanja, zanimanja i aktivnosti. Etiologija ove skupine poremećaja je još uvijek nepoznata, iako je velik broj istraživanja posvećen otkrivanju njihova uzroka. Istraživanja su usmjerena prema različitim aspektima autizma - genskim čimbenicima, morfologiji mozga, somatskim poremećajima u djece s autizmom, kao i utjecaju pre i perinatalnih čimbenika rizika u djece s autističnim spektrom poremećaja. Ova istraživanja bi mogla dovesti do otkrića ranih biomarkera korisnih u kliničkoj praksi, koji bi mogli dovesti do ranog otkrića poremećaja. Do tada, važno je istaknuti rane kliničke znakove autizma, čije bi prepoznavanje moglo dovesti do poboljšanja konačnog ishoda poremećaja. U ovom članku donosimo sažetak kliničkih manifestacija poremećaja autističnog spektra, rezultate istraživanja različitih aspekata etiologije, a ujedno i skrećemo pozornost na rane znakove autizma, uz naglasak na važnost uloge pedijatra u ranom otkrivanju ove skupine poremećaja.

Deskriptori: AUTISTIČNI SPEKTAR, ETIOLOGIJA, DJECA