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RECENT STUDIES ON GENETIC AND ENVIRONMENTAL BASIS OF AUTISM

OTİZMİN GENETİK VE ÇEVRESEL TEMELLERİ HAKKINDAKİ SON ÇALIŞMALAR

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Abstract

Autism is a childhood neurodevelopmental disorder that affects 1–2 in 100 children, according to recent data on the broad array of autism spectrum disorders. It is a neurodevelopmental disorder, genetic and environmental factors playing role in autism. Molecular and mechanistic basis of autism started to be enlightened. As a genetic basis of disease, glutamate gene mechanisms supposed to develop a new method for diagnosing and treatment of autism. Aim of this mini-review is to gain a general knowledge about genetic and environmental reasons of autism.

Keywords: autism, glutamate, immune system, genetic, neurodevelopment.

Özet

Otizm, son verilere gore, 100 çocuktan 1-2 sinde görülen bir çocukluk çağı nörogelişimsel hastalığıdır.Nörogelişimsel bir hastalık olan otizmde genetik ve çevresel faktörler rol oynar. Otizmin moleküler ve mekanistik temelleri aydınlatılmaya başlanmıştır. Hastalığın genetik altyapılarından biri olarak, glutamat gen mekanizması, teşhis ve tedavisi için yeni bir metod geliştirilmesine olanak sağlayabilir. Bu kısa derlemenin amacı, otizmin genetik ve çevresel nedenleri ile ilgili yapılan son çalışmalardan faydalanılarak hastalık hakkında bilgi edinmektir.

Anahtar Kelimeler: *otizm, glutamate, immune system, genetik, nörogelişim*

1. Introduction

Autism is a neurodevelopmental disorder that affects 1–2 in 100 children, according to recent data on the broad array of autism spectrum disorders. Autism is diagnosed when a child or adult has abnormalities in a ''triad'' of behavioral domains: social development, communication, and repetitive behavior/obsessive interests. Autism can occur at any point on the IQ continuum, and IQ is a strong predictor of outcome (Baron-Cohen et al., 2009). Unusual social development becomes apparent early in childhood. Autistic infants show less attention to social stimuli, smile and look at others less often, and respond less to their own name. Autistic toddlers differ more strikingly from social norms; for example, they have less eye contact and turn taking, and do not have the ability to use simple movements to express themselves, such as the deficiency to point at things.

Autism is one of the subtypes of autism spectrum disorders (ASD) which refers to a group of childhood neurodevelopmental disorders with polygenic etiology. The disorders are characterized by impaired social interaction, communication and verbal communication and language impairments, and repetitive behaviors and interests. Autism has an increasing prevalence in recent years. From 2007 to 2011–2012, the incidence of ASD rose from 1.16% to 2.00% in the United States of America (Blumberg et al., 2013).

Most researches show that both genetic and environmental factors play a role in the development of ASD. High concordance of ASD among boys and girls cannot be explained by genetic heritability alone; shared environmental factors explain a large proportion of the variance in liability. In addition, prenatal exposure to organophosphates has been related to a significant reduction in childhood IQ.

2. Glutamate and Autism

Glutamate is a major excitatory neurotransmitter, is highly concentrated throughout the brain and is crucial to neuronal plasticity and the maintenance of cognitive

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functioning. However, excess glutamate has been shown to be a potent neurotoxin that leads to neuronal cell death (Manev et al., 1989) and is deemed to play a role in the pathophysiology of some neuropsychiatric disorders (Sheldon et al., 2007). Recently, a hyperglutamatergic hypothesis of autism was proposed (Blaylock et al., 2009) based on evidence of hyperglutamatergia in the brain of individuals with autism. For instance, in a study, levels of GAD 65 kDa and GAD 67 kDa proteins, both of which are involved in converting glutamate to GABA, are reduced in the brains of individuals with autism, resulting in increased levels of glutamate in the brain substrate (Fatemi et al, 2002). In addition, in another study that contains neuroimaging magnetic resonance spectroscopy has demonstrated that individuals with ASD have significantly higher concentrations of glutamate in the amygdala- hippocampal region than do healthy controls (Page et al., 2006). The high level of plasma glutamate level especially in children with normal IQ is supposed to be biomarker to diagnose autism (Shimmura et al., 2011). Higher glutamate level is not limited to plasma, and some studies confirmed its higher level in some brain regions (amygdala-hippocampal regions) of patients with autism compared to the controls (Page et al., 2006).

Most psychiatric and neurodevelopmental disorders (PNDD) have a strong heritable component (Sullivan et al., 2012). Twin studies have proved that neurodevelopmental disorders, such as (ASD) (Posthuma et al., 2013). Glutamate receptors (GluRs) mediate excitatory synaptic transmission and plasticity in the brain (Traynelis et al., 2010). Glutamate receptors encode GRIK2, GRIN3B and GRIA3 genes which are related to ASD. In addition, anomalies in regions on chromosomes six and seven, encoding Glu receptors, have been related to ASD (Yang et al., 2013). Abnormalities in the glutamatergic system might therefore be implied in ASD. Indeed, epileptic seizures which have been related to excitatory Glu and decreased GABA, are common in ASD (Ballaban et al., 2000).

3. Effects of environmental factors against autism

In addition to genetic basis of glutamate level, environmental components also play role increased glutamate level children with autism. Many children with autism are picky eaters. They do not like a variety of different foods. Eating problems are risk factors for nutritional deficiencies. Some of these children do not like to try new foods and have food selectivity (Kral et al., 2013).

Last findings support that many children with autism suffer from amino acids metabolism impairment. Nearly, all the studies reported higher levels of plasma glutamate in children with autism than those of the controls. Hyperglutamatergic state causes excitotoxicity and neurodegeneration (Sheldon et al., 2007). Moreover, this increased glutamate level is compatible with the findings that the level of proteins involved in transforming glutamate to GABA is decreased. A study compared plasma level of 25 amino acids between high-functioning autism children and the healthy controls. The study showed that only the levels of glutamate and glutamine were different between the two groups. While the level of glutamate was increased, the level of glutamine was decreased (Shimmura et al., 2011).

4. Immunologic system and autism

There is increasing evidence supporting that an immune insult during pregnancy can have a significant effect on the developing fetus (Brown, 2012). For over 30 years, epidemiological research has continued to find associations between maternal infection and increased risk of autism (Atladottir et al., 2010). A recent large case-control population based study revealed an increased risk of developing autism spectrum disorder (ASD) with maternal fever, which was attenuated if pregnant mothers used a fever reducing agent (Zerbo et al., 2013). In addition, reports highlight associations between risk of having a child with autism and increased levels of inflammatory mediators in both the maternal sera and amniotic fluid. These increased inflammatory markers, interleukins (IL)-4, IL-5, and interferon (IFN)-γ. (Abdallah et al., 2012), supporting a relationship between maternal immune activation (MIA), aberrant fetal neurodevelopment, and risk for neurodevelopmental disorders such as autism. Also inflammatory markers are playing role in other neurological disorders such as panic disorder. A supporting study has shownIL-12and IFN-γ were significantly lower in panic disorder group when compared to the controls and IFN-γ values were significant predictors of the presence of panic disorder (Tukel et al., 2012).

5. Conclusion

Autism is not only resulting from genetic factors but also environmental factors play significant role in the development of autism. From the beginning of individual's existence all factors can be effective. There are many questions waiting to be answered about autism. Is it an untreatable genetic destiny? Is there a chance to diagnose autism before childhood?

It is still nebulous the underlying mechanisms of autism. With understanding the role of molecular and mechanistic basis of autism more details will be enlightened about disease. Glutamate mechanism is only one of the molecular reasons of autism. All knowledge in this area, throw a new light on developing new genetic treatment methods.

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