BMH MEDICAL JOURNAL

BMH Med. J. 2018;5(2):57-62 **Review Article**

Autism Spectrum Disorder – Advances in Genomics and Impact of Early Behavioral Intervention

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Abstract

Autism spectrum disorder is a developmental disorder characterized by persistent deficits in social interaction and communication. It is also associated with restricted, repetitive patterns of behavior or activities. It is a complex polygenic disorder which occurs due to altered gene-environmental interaction. There are several single nucleotide polymorphisms associated with autism spectrum disorder. Copy number variations are detected in several autism spectrum disorder probands. Recent studies have found novel candidate genes and point mutations associated with this disorder. Abnormal synaptic homeostasis is found to be a risk factor for autism spectrum disorder. Several risk genes are the key regulators of synaptic plasticity. Rare de novo and inherited copy number variations have been implicated in the genetic risk factors. The key to successful management of autism spectrum disorder is early behavioral intervention. Infant "at risk" should be provided very early intervention before full syndrome is present. Parent training interventions have an important role in the management of these children. Early interventions will improve the intelligence, adaptive behavior as well as the social and communication skills of the children with autism spectrum disorder.

Keywords: Autism Spectrum Disorder, Genomics, Early Behavioral Intervention

Introduction

Autism spectrum disorder (ASD) is an early onset developmental disorder affecting communication skills and social interaction. It is also associated with repetitive and stereotypic behaviors. There are two distinct subcategories within restricted and repetitive behaviors in ASD which include repetitive sensory motor behaviours and insistence on sameness [1]. ASD is the fastest growing developmental disorder in the recent years. The prevalence of ASD has now reached ratios up to 1 in 68 children. This disorder is seen four times more frequently in boys compared to girls [2]. If not intervened at the earliest, autism spectrum disorder is a disabling developmental disorder because the deficits in communication and socialization as well as the stereotyped repetitive behaviors will persist throughout the life of the individual.

ASD occurs due to altered gene-environmental interaction. Fetuses and infants with vulnerable

genes when exposed to environmental risk factors are prone to develop ASD. There is strong evidence suggesting genetic link for ASD. Several genes associated with neuronal synaptic function are involved in the development of this disorder. Linkage studies have found several single nucleotide polymorphisms associated with autism spectrum disorder [3]. Hundreds of causative and susceptible genes, linkage regions and microRNAs have been associated with this complex genetic disorder [4].

Recent advances in genomic technologies have led to the discovery of submicroscopic chromosomal changes known as copy number variations (CNVs) in autism spectrum disorder [2]. The genome variability in individuals occur due to microdeletions and microduplications that are undetectable at the level of traditional cytogenetic analysis. These alterations are collectively termed as copy number variations. These may have no phenotypic effect but can underlie the disorder. In the CNV map of the human genome, 4.8-9.5% of the genome contributes to copy number variations. There are about 100 genes that can be completely deleted without causing phenotypic consequences [5]. De novo copy number variations and single nucleotide variants are detected in several ASD probands. Recent studies have identified novel candidate genes and point mutations in sporadic cases [3].

The etiology of ASD is complex. Both genetic and environmental factors contribute to the individual liability. Because of brain plasticity, early interventions lead to reversal of symptoms in toddlers with ASD. In order to improve the quality of life of children with ASD, there has been an increasing focus on early detection and early intervention of ASD, from the scientific field and also from professional associations, during the last decade [6]. Behavior problems and secondary neurological problems in ASD can be prevented by early behavioral intervention, because of early brain plasticity.

Early behavioural intervention is the key to successful management of autism spectrum disorder. Early intervention programmes improve the developmental functioning and correct the maladaptive behaviours in children with ASD [7]. Early intensive behavioral intervention should be started for children at risk for autism spectrum disorder without waiting for a diagnosis. This will avoid long waits for diagnostic evaluation and will lead to maximum improvement in the outcome [8].

Advances in Genomics in Autism Spectrum Disorder

Autism spectrum disorder is a complex polygenic disorder. Advances in genomics have found that de novo mutations account for many cases of ASD. The genome-wide genotyping and sequencing techniques have led to significant advances in finding out the genetic architecture of risk for ASD. Rare de novo and inherited variations acting within the common-variant genetic load accounts for the majority of ASD liability [9]. Copy number variations are associated with increased risk of autism spectrum disorder. CNVs also contribute to the heterogeneity of ASD phenotypes [2, 10].

Copy-number variants contribute significantly to ASD risk in families with only one affected child. These are called simplex families. In families with multiple affected individuals (multiplex families) the contribution of both de novo and inherited CNVs to ASD is not very significant. This indicates that other factors are also contributing to ASD risk in multiplex families. A rare risk locus for ASD in multiplex families is found at chromosomal region 2q24 [11].

Though rare de novo and inherited copy number variations have been implicated in ASD risk, the genetic basis of ASD is not known in more than 80% of cases. Several CNVs are found in ASD regions like Glutathione S-Transferase Mu1-5, Fragile Histidine Triad (FHIT), neuronal RNA binding protein (Rbfox1), the alpha 7 neuronal nicotinic acetylcholine receptor gene (CHRNA7), 15q11.2, 15q13.2-q13.3, 17q12, and 22q11.21. Through gene prioritization, several new candidate genes like bradykinin B1 recepter gene (BDKRB1), bradykinin B2 recepter gene (BDKRB2), cytochrome P450 2E1 (CYP2E1), phospholipase C delta 3 (PLCD3), ubiquinol-cytochrome-c

reductase core protein 2 (UQCRC2), leucocyte Ig-like receptor B3 (LILRB3), ribosomal protein S9 (RPS9) and COL11A2, encoding collagen type XI alpha-2 are identified and these new candidate genes may contribute to the genetic architecture of autism spectrum disorder [12]. CNVs affecting PARK2 gene function may lead to the genetic etiology of some of the individuals with ASD [13].

Abnormal synaptic homeostasis is a risk factor to ASD. Several risk genes linked to autism spectrum disorders are the key regulators of synaptic plasticity. Many of these risk genes encode synaptic scaffolding proteins and the proteins involved in chromatin remodeling. Changes in these proteins can alter the synaptic strength or number. This in turn can alter the neuronal connectivity in the brain. Deleterious mutations can cause impaired synaptic homeostasis [14].

High-throughput next-generation sequencing has recently revealed novel risk genes [15]. SHANK (SH3 domain and ankyrin repeat containing) family of proteins act as scaffold proteins that are necessary for the development and function of neuronal synapses. Several genomic studies have found an association between autism spectrum disorder and mutations in the SHANK1, SHANK2 and SHANK3 genes, which are present at glutamatergic synapses in the central nervous system. Disruption of SHANK scaffolding proteins can affect the structure and function of neural circuits and lead to alteration in behaviour [16]. Neurexins are presynaptic single-pass transmembrane proteins which function as synaptic organizers. They mediate the conduction of nerve signals. Genomic alterations in neurexins are identified in autism spectrum disorder. The neurexins consist of three genes (NRXN1, NRXN2, and NRXN3) which are candidate genes for ASD [17].

The genetic risk of ASD is influenced by polygenic and de novo variation. In individuals with ASD who carry a strongly acting de novo variant, polygenic variation contributes additively to the risk [18]. Although lots of advances are made in genomics related to ASD, only about 10% of children with ASD have an identifiable genetic condition [19].

Impact of Early Behavioural Intervention

Impairments in neuronal connectivity during very early childhood lead to autism spectrum disorder. During the last decade, there has been increasing focus on early detection of autism spectrum disorder from the scientific field and also from public health systems. To offer better quality of life for children with ASD, several screening procedures are developed for early detection [6]. Behavioral markers of ASD can be identified even in infancy [20].

Delays in social communication behaviours like anticipatory social response, orientation to name and eye contact as well as non-social behaviours like disengagement of visual attention are behavioural markers for autism in infancy [21]. The most frequent early signs of ASD include atypical visual tracking, lack of social reciprocity, uncoordinated eye contact and lack of social smile. Delayed development of nonverbal communication and delay in development of joint attention are also early signs of ASD [22].

Early interventions are most effective if started before two years of age because it will have significant effect on the plasticity of the developing brain. This in turn will promote early learning and provide opportunity for changing the neuronal connectivity in children with ASD. Early behavioral intervention leads to normalized patterns of brain activity and it is essential for improving the prognosis of ASD [22].

The only well-established treatment for young children with autism spectrum disorder is early intensive behavioral intervention [23]. Early identification and intervention will improve outcomes in children at risk for ASD [24]. Early intensive behavioral and developmental interventions lead to improvements in cognitive performance, communication skills and adaptive behavior in young

children with autism spectrum disorder. Specific parent-training interventions will lead to gains in language and social functions and help to overcome the challenging behaviors in these children [25].

The early interventions should be individualized to each child's behavioral profiles, level of language development as well as adaptive functioning. The support and involvement of the parents and other family members are very important. The early intervention program mainly focus on remediating the core deficits of ASD such as impairments in communication skills as well as social skills and the behavioral problems. Early developmental and behavioral interventions lead to reduction in the core symptoms and also increases the intelligence, adaptive behavior and language skills of the children with autism spectrum disorder [22].

Parent training interventions are currently being emphasized increasingly, because if parents are taught scientifically how to deliver individualized interventions to their child at home, there will be significant improvement in a wide variety of social and communication skills. Parent mediated interventions also reduce the stereotyped repetitive behaviors within the family context. Parent-implemented interventions improve the developmental outcomes in the language domain as well as social communicational behaviors in toddlers with ASD [26].

With early detection and early behavioral interventions, even prevention of ASD is possible. To prevent the children from becoming autistic, very early interventions should be given to the infants at risk before the full syndrome is present [27].

Beginning the early interventions in infancy or toddlerhood is always the best, because of brain plasticity in infancy and toddlerhood. This will definitely reduce the burden of social and communication impairment and will significantly enhance the quality of life of these children. Individualized early intensive behavioural intervention should be provided for all children with autism spectrum disorder [28].

Conclusion

Autism spectrum disorder is a developmental disorder characterized by persistent deficits in communication and social interaction, associated with restricted repertoire of behavior and interests. The prevalence of ASD has increased significantly over the last few decades. The incremental trend in autism spectrum disorder is a global phenomenon. ASD occurs due to complex interactions between genes and environment which in turn alter the brain functions. Advances in genomics have recently revealed many novel risk genes. De novo mutations account for many cases of ASD. Copy-number variants also contribute significantly to ASD risk.

Early behavioral intervention has great impact in changing the developmental trajectories of the brain in children with autism spectrum disorder. Parent training interventions will improve the social skills and communication skills in at risk infants and in toddlers with ASD. Due to brain plasticity in infancy and toddlerhood, early intervention will improve the social and communication skills and will significantly reduce the behavior problems, which in turn improves the quality of life of these children. Hence very early intervention should be given to at risk infants before the full symptoms manifest. All children with autism spectrum disorder should be given early intervention in toddlerhood.

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