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Review

Autistic spectrum disorders: A review of clinical features, theories and diagnosis

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ABSTRACT

Autism spectrum disorder (ASD) is a set of neurodevelopmental disorders that is among the most severe in terms of prevalence, morbidity and impact to the society. It is characterized by complex behavioral phenotype and deficits in both social and cognitive functions. Although the exact cause of ASD is still not known, the main findings emphasize the role of genetic and environmental factors in the development of autistic behavior. Environmental factors are also likely to interact with the genetic profile and cause aberrant changes in brain growth, neuronal development, and functional connectivity. The past few years have seen an increase in the prevalence of ASD, as a result of enhanced clinical tests and diagnostic tools. Despite growing evidence for the involvement of endogenous biomarkers in the pathophysiology of ASD, early detection of this disorder remains a big challenge. This paper describes the main behavioral and cognitive features of ASD, as well as the symptoms that differentiate autism from other developmental disorders. An attempt will be made to integrate all the available evidence which point to reduced brain connectivity, mirror neurons deficits, and inhibition–excitation imbalance in individuals with ASD. Finally, this review discusses the main factors involved in the pathophysiology of ASD, and illustrates some of the most important markers used for the diagnosis of this debilitating disorder.

Contents

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1. Introduction

The autism spectrum disorder (ASD) describes a wide range of symptoms, including difficulty with social interaction and communication skills, as well as unusually repetitive behavior (American Psychiatric Association, 2013). According to the diagnostic and statistical manual of mental disorders, 5th edition (DSM-5), individuals with ASD have a tendency to respond inappropriately in conversation and lack the ability to build relationships (American Psychiatric Association, 2013). They often engage in a series of abnormal routines and develop inappropriate obsessions on particular items (American Psychiatric Association, 2013). Individuals with ASD also display a wide variety of cognitive functioning, ranging from severe intellectual disability to superior intelligence (Grzadzinski et al., 2013). However, the DSM-5 does not consider delays in language acquisition to be part of the core symptoms of ASD because this characteristic is not universal to individuals with this disorder (American Psychiatric Association, 2013; Grzadzinski et al., 2013). Among all the diseases from the autism spectrum, autism is undoubtedly the most severe, and can be distinguished from other neurodevelopmental conditions such as Asperger's syndrome (AS) and pervasive developmental disorder not otherwise specified (PDD–NOS) by the delay in language development and the severity of behavioral and intellectual impairments (Levy et al., 2009; Szpir, 2006).

Approximately 20 per 10,000 children are affected by ASD, and the early symptoms of this disorder can be identified from the age of 1 to 3 years old (Levy et al., 2009; Newschaffer et al., 2007). Although the exact cause of ASD is still not known, it is believed that both genetic and environmental factors influence the onset and development of this disorder (Lai et al., 2014; Tordjman et al., 2014). Interaction between multiple genetic variants and epigenetic factors also increase the risk of having ASD (Tordjman et al., 2014). In terms of financial cost, ASD can be a heavy burden to the family of affected children (Newschaffer et al., 2007). Over the life of a child, expenses can go up to US $2.4 million per family, due to special education services by psychologists and speech therapists, and the added expenses of technology-based therapies (Buescher et al., 2014). Moreover, children with ASD often have comorbid medical conditions, including intellectual disability, seizure, anxiety and depression (Gillott et al., 2001; Newschaffer et al., 2007; Tuchman and Rapin, 2002). Therefore, early detection of this disease is crucial since it could help a child with ASD make significant gains in language and social skills. In this review, a closer look will be given at the clinical features and underlying causes of ASD, as well as the tools commonly used to diagnose this neurodevelopmental disorder.

2. Clinical features and symptoms of ASD

ASD can be distinguished by a pattern of multiple symptoms, and is typically identified before 2 years of age (Mazurek et al., 2014). The symptoms of ASD are classified into two broad categories: the core and the secondary symptoms (American Psychiatric Association, 2013). The core symptoms consist of reduced language skills and social interaction, as well as the presence of repetitive and stereotypic behaviors (American Psychiatric Association, 2013; Weitlauf et al., 2014). In contrast, secondary symptoms include complications such as self-injury, hyperactivity, aggression, and co-occurring psychiatric disorders such as anxiety and major depression (Dosreis et al., 2006; Kaat et al., 2013; Kim et al., 2011). These symptoms often change depending on the age of the affected individual. Indeed, most individuals with ASD have language deficits and problems with hyperactivity during early childhood, but experience problems with relationships and mood regulation during adolescence (Nazeer and Ghaziuddin, 2012). Moreover, during late adolescence and early adulthood, up to 17% of affected individuals develop catatonia, a potentially life-threatening condition characterized by neurogenic motor and behavioral abnormalities (Stoppelbein et al., 2006; Wing and Shah, 2000).

3. Theories of ASD

3.1. Theory of impeded plasticity

It is widely known that the brain of autistic children presents functional and morphological dysfunctions. Studies using functional magnetic resonance imaging (fMRI) have already demonstrated a significant reduction in long-distance connectivity in the brains of ASD individuals (Dichter, 2012; Just et al., 2012). At the microstructural level, disruption of brain development is caused by abnormal regulation of cell division and apoptosis, as well as increased neuronal inflammation (Polsek et al., 2011). Recently, it has been shown that patterns of both hypo- and hyper-connectivity could be observed in the brain of autistic children (Kana et al., 2014; Muller et al., 2011). This difference in hypo- and hyper-connectivity depends on age-related factors (Kana et al., 2014). A study reported that at 3 months old, children who are at high risk for developing autism show increased connectivity compared to low-risk children, and that this difference starts to gradually disappear between the age of 6 and 9 months (Keehn et al., 2013). There is also evidence suggesting that the autistic brain is characterized by morphological abnormalities such as early overgrowth of several brain structures including the frontal cortex, the amygdala and the cerebellum (Polsek et al., 2011). Indeed, 6 months after birth, the head circumference of infants with ASD grows rapidly compared to normal infants, but starts to decrease during late childhood, resulting in normal adult brain volume and size (Courchesne et al., 2003; Herbert et al., 2003).

3.2. Excitation and inhibition dysregulation

Balanced development of excitatory and inhibitory synapses is essential for the normal function of sensory and cognitive networks in the brain (Takahashi et al., 2012). An imbalance in this development may cause the pathogenesis of several neuropsychiatric disorders, including ASD, schizophrenia and bipolar disorder (Takahashi et al., 2012). In the mature central nervous system, amino butyric acid (GABA)-interneurons send inhibitory synaptic inputs, while glutamatergic neurons send excitatory inputs. Mutations and environmental factors that increase glutamate signaling or decrease GABAergic signaling could lead to an imbalance of excitation and inhibition, and could therefore increase the risk to ASD (Rubenstein and Merzenich, 2003). There is a significant amount of studies suggesting that individuals with ASD have higher than normal glutamate blood levels (Aldred et al., 2003; Shimmura et al., 2011). GABA, which plays a key role in regulating neuronal excitability, is also found altered in individuals with ASD (Pizzarelli and Cherubini, 2011; Blatt and Fatemi, 2011). Alterations in the GABAergic level in the brain of autistic individuals may account for several clinical phenotypes including the development of epileptic seizures and intellectual disabilities (Blatt and Fatemi, 2011). Overall, evidence suggests that there is a marked dysregulation of the excitatory glutamate system and inhibitory GABA system in the brain of individuals with ASD. However, it is still not very well known how these synaptic inputs influence neuronal circuitry and social behavior. Clearly more comprehensive behavioral and electrophysiological studies need to be done to help better define