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Recent update of autism spectrum disorders

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In patients with a language developmental delay, it is necessary to make a differential diagnosis for autism spectrum disorders (ASDs), specific language impairment, and mental retardation. It is important that pediatricians recognize the signs and symptoms of ASDs, as many patients with language developmental delays are ultimately diagnosed with ASDs. Pediatricians play an important role in the early recognition of ASDs, because they are usually the first point of contact for children with ASDs. A revision of the diagnostic criteria of ASDs was proposed in the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* (DSM-5) that was released in May 2013. The autism spectrum describes a range of conditions classified as neurodevelopmental disorders in the fifth edition of the DSM. The new diagnostic criteria encompasses previous elements from the diagnosis of autistic disorder, Asperger disorder, childhood disintegrative disorder, and pervasive developmental disorder-not otherwise specified. An additional change to the DSM includes synthesizing the section on social and communication deficits into one domain. In ASD patients, the appropriate behavioral therapies and rehabilitation treatments significantly affect the prognosis. Therefore, this makes early diagnosis and treatment very important. In conclusion, pediatricians need to be able to recognize the signs and symptoms of ASDs and be attentive to them in order to make an early diagnosis and provide treatment.

Key words: Autism spectrum disorder, Developmental disabilities, Genetics

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Introduction

In Korea, the national health screening program for infants and children (zero to six years of age) has been implemented since November 2007, to monitor the growth and development of infants and children as well as to provide parents with appropriate education programs. For children aged 9 months, 18 months, 30 months, and 5 years, the Korean-Ages and Stages Questionnaire (K-ASQ) and the Denver-II developmental assessments are used. When infants or children show questionable scores, they are referred to professional institutions for a confirmatory diagnosis of developmental delay. According to the report on the effects of the health screening for infants and children, developmental delays were suspected in 0.6%–2.5% of the children tested and 99% of these children were diagnosed with neurodevelopmental disorders. The final distribution of diagnoses included global developmental delay (50%), developmental language disorder (26%), cerebral palsy (10%), motor developmental delay (9%), and autistic disorders (4%)[1].

Among the developmental disorders, developmental language disorder was the second most common; in addition, many autism spectrum disorders (ASDs) were reported. In language delay patients, it is necessary to make a differential diagnoses for ASDs, specific language impairment, and mental retardation. It is important that pediatricians recognize the signs and symptoms of ASDs as many patients with language developmental delays are ultimately diagnosed with ASDs. Pediatricians play an important role in the early recognition of ASDs, because they are usually the first point of contact for patients.

The ASDs represent a wide continuum of associated cognitive and neurobehavioral deficits, including deficits in socialization and communication, with restricted and repetitive patterns of behavior. ASDs are organic neurodevelopmental disorders caused by genetic or neurobiological factors rather than by psychological or environmental ones. Recently, many studies on the genetics of ASDs have been conducted. In the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* (DSM-5), published in May 2013, the diagnostic criteria for ASDs have subsequently been revised.

In this article, the most recent diagnostic criteria and the latest research on genetic studies with ASDs have been reviewed.

Historical background

Kanner[2] first documented a syndrome of "autistic disturbances" in 11 children who shared previously unreported patterns of behavior, including poor social interaction, obsessiveness, stereotypic movement, and echolalia. Autism, the prototypic pervasive developmental disorder (PDD), is characterized by an onset prior to 3 years of age and by a triad of behavioral signs and symptoms, including (1) abnormal development in the use of language; (2) lack of reciprocal social interaction and responsiveness; and (3) restricted, stereotypical, and ritualized patterns of interests and behavior[3].

The *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (DSM-IV; 1994) and the DSM-IV-TR (text revision; 2000) included five possible diagnoses under the PDD: autistic disorder, Asperger disorder, childhood disintegrative disorder, Rett syndrome, and PDD-not otherwise specified (NOS). A revision of the ASDs was proposed in the DSM-5, released in May 2013[4]. The autism spectrum describes a range of conditions classified as neurodevelopmental disorders in the fifth edition of the DSM. The new diagnosis encompasses the previous diagnostic criteria for autistic disorder, Asperger syndrome, childhood disintegrative disorder, and PDD-NOS.

It is believed that individuals with ASDs are best represented as a single diagnostic category because they show similar types of symptoms and are better differentiated by clinical specifiers (i.e., dimensions of severity) and associated features (i.e., known genetic disorders, epilepsy, and intellectual disability). An additional change to the DSM-5 includes synthesizing the social and communication deficits section into one domain.

Diagnostic criteria

The diagnostic criteria of autism in the DSM-IV consisted of three domains: social interaction impairment, communication deficits, and stereotypic behavior. These were condensed into two domains in the DSM-5: deficits in social communication and restricted patterns of behavior (Table 1). Additionally, the autism categories in the DSM-IV included autistic disorder, Asperger disorder, Rett syndrome, childhood disintegrative disorder, and PDD-NOS. However, these were converted to only one category in the DSM-5: ASD, with various severity levels added (Table 2).

Table 1. DSM-5 diagnostic criteria for autism spectrum disorders

DSM-IV
Social impairment
Speech/communication deficits and language delay
Repetitive behaviors and restricted interests
DSM-5
Deficits in social communication
Restricted, repetitive patterns of behavior, interests

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition.

Table 2. Categories of autism spectrum disorders

DSM-IV
Pervasive developmental disorders (PDD)
Autistic disorder
Asperger disorder
Rett syndrome
Childhood disintegrative disorder
PDD-not otherwise specified
DSM-5
Autism spectrum disorder
Level 3: Requiring support
Level 2: Requiring substantial support
Level 3: Requiring substantial support

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition.

Epidemiology

The prevalence of autism has increased dramatically, and it has been currently recognized as one of the most common developmental disorders. For many years after autism was first described in the 1940s, its prevalence was considered to be two to four cases per 10,000 children[5].

Based on the most recent United States diagnostic survey reported by parents, the prevalence of ASD was as high as 11 per 1,000[6]. A number of factors have contributed to this increase. The diagnostic criteria for ASDs have been broadened; the concept of autism is now defined as an autistic disorder plus the broader ASDs, including Asperger syndrome and PDD-NOS. There is also

a codiagnosis with known medical disorders such as fragile X syndrome, Tourette syndrome, and Down syndrome. Additionally, the growing public awareness among parents and teachers in developing countries has led to earlier diagnoses. Other factors include the increased availability of services and the ability to diagnose children at younger ages[7,8].

Pathophysiology and etiology

1. Genetics

The known single-gene defects and the diagnosed medical conditions account for about 10% of the cases of autism[9]. Between 21% and 50% of the boys with fragile X syndrome are on the autistic spectrum[10], and 0%–6% of the autism populations have fragile X syndrome[11].

The prevalence rates of ASD in tuberous sclerosis complex (TSC) consistently range from 24% to 60%[10]. The incidence of autistic individuals with TSC complex has been estimated to be between 0.4% and 4% in epidemiologic studies[12].

Copy number variants (CNVs) are DNA segments ranging in size from 50 base pairs to several megabases among individuals due to deletion, insertion, inversion, duplication, or complex recombination[13]. Recently, it has been demonstrated that the CNV location and its functional relevance may play a more crucial role than the mean CNV number and size.

Recently, two large datasets have been discovered: heterogeneous *de novo* copy-number variants collectively affecting several loci and presumably accounting for 5%–8% of the cases of simplex forms of ASD[14]. The network-based functional analysis of these rare CNVs confirms the involvement of these loci in synapse development, axon targeting, and neuron motility[15].

Several neuroligins and *SHANK* and neurexin genes encoding proteins crucial to synapse formation, maturation, and stabilization have been found to host mutations responsible for behavioral phenotypes, including autism[16]. At the extracellular level, postsynaptic neuroligins interact with presynaptic or neurexins stimulating the formation of the presynaptic bouton[17]. At the intracellular level, neuroligins associate with postsynaptic scaffolding proteins such as SHANK3[18]. Neuroligins are encoded by the *NLGN1, NLGN2, NLGN3, NLGN4X,* and *NLGN5* genes. Among them, only the *NLGN3, NLGN4,* and *NLGN4Y* genes have been found to harbor mutations that could possibly cause autism.

Three members of the *SHANK* gene family (*SHANK1, SHANK2,* and *SHANK3*), which encode the scaffolding proteins are required for the proper formation and function of neuronal synapses. Recently, SHANK2 mutations have also been reported in both ASD and intellectual disability[19].

The third crucial protein in the autism-related synaptic network is neurexins, encoded by the three highly conserved genes: *NRXN1, NRXN2,* and *NRXN3*.

The *MECP2* gene is important for the correct brain function and development: loss of MECP2 has been shown to delay neuronal maturation and synaptogenesis, and MECP2 *de novo* loss-of-function mutations cause Rett syndrome in approximately 70% of the affected females, while they are generally found to be lethal in males[20].

Children with idiopathic autism often display minor facial dysmorphisms and abnormal head/body growth rates[21,22]. Macrocephaly is seen in approximately 20% of children with autism[22]. The *Hox* genes play a crucial role during embryonic patterning and organogenesis. The phosphatase and tensin homolog (*PTEN*) gene located in chromosome 10q23, harbors mutations associated with a broad spectrum of disorders, including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, and Lhermitte-Duclos disease[23].

PTEN is a tumor suppressor gene that favors cell cycle arrest in G1 and apoptosis. Genetic syndromes linked to PTEN germline haploinsufficiency are often associated with autism or mental retardation[24].

The eukaryotic translation initiation factor 4E gene (*EIF4E*, located on chr. 4q21-q25) plays a pivotal role in protein translation downstream of mammalian target of rapamycin. Recently, a balanced translocation disrupting the EIF4E locus was found in a boy with ASD demonstrating regression of language and social interactions at 2 years of age[25].

Recent genetic evidence proposes that at least some ASD cases may result from abnormal Ca^{2+} homeostasis during neurodevelopment[26]. Moreover, several genetic studies have found autism-related genes encoding proteins either directly or indirectly, controlling intracellular Ca^{2+} levels or regulated by cytosolic Ca^{2+} transients. The biochemical parameters linked to the mitochondrial function are frequently abnormal in autism[27]. It is only in rare instances that mutations in mitochondrial DNA or in nuclear DNA heavily involved in the mitochondrial function explain the disease. Children with mitochondrial disease thus, represent a small percentage (<1%) of all autistic patients. In reality, mitochondrial ASD forms are rare, as mitochondrial dysfunction appears to be secondary in most patients—i.e., downstream of other pathophysiological abnormalities such as excessive oxidative stress[28].

2. Environmental factors

The expression of the autism gene may be influenced by environmental factors[29]. According to the epigenetic theory, environmental factors may modulate the already existing genetic factors responsible for the manifestation of ASDs in individual

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children. The increasing age of mothers is a risk factor of ASD, both independently and in combination with the increasing age of fathers[30].

There may also be mutagens in the environment, such as mercury, cadmium, nickel, trichloroethylene, and vinyl chloride. The factors associated with vitamin D deficiency may cause mutations, as vitamin D contributes to the repair of DNA damage [31].

3. Brain imaging

Ninety percent of children with autism had an above average brain volume at 2–4 years old and 37% had developmental macrocephaly, defined as a brain volume exceeding 2 standard deviations above the mean normal for that particular age[32]. This finding reveals an ongoing postnatal process that primarily affects the interhemispheric and cortical connections.

The results of the recent functional magnetic resonance imaging studies point to changes in the activation and synchronization of cortical networks. The functional connectivity of the networks is lowered, leading to deficits in language, social cognition, motor planning, and perception[33].

4. Neuropathology

Kemper and Bauman[34] described three major findings in children with autism: (1) curtailment of the normal development of the forebrain neurons, which were smaller and more densely distributed than normal; (2) an apparent congenital decrease in the number of Purkinje cells; and (3) age-related changes in cell size and in the number of neurons in the diagonal band of Broca, the cerebellar nuclei, and the inferior olive.

Clinical features

All individuals on the autistic spectrum demonstrate impairments in three symptom domains: reciprocal social interactions, verbal and nonverbal communication, and restricted and repetitive behaviors or interests. The cognitive function of ASD patients can range from profound mental retardation to the superior range on the conventional intelligence quotient tests.

1. Impairment of social interactions

ASD infants may or may not cuddle, or may even stiffen when held, and often do not look at the person or smile when interacting socially. Older children often do not point things out or use eye contact to share the pleasure of seeing something with another person, which is called joint attention or social referencing. Deficits in joint attention appear to be among the primary distinguishing characteristics of children with ASD[35].

Children with autism may appear to ignore a familiar or unfamiliar person because of a lack of social interest. They may also have no age-appropriate friends and may prefer to play alone.

2. Impairment of communication

The expressive language function across the autistic spectrum ranges from complete mutism to verbal fluency. In early infancy, some children with ASD do not babble or use any other communicative vocalization, and are therefore, described as "quiet babies." Moreover, they cannot compensate for this language deficit with facial expressions or gestures. A hallmark of autistic speech is immediate or delayed echolalia. Some children with autism do not use toys, animals, or dolls in pretend play appropriately. In addition, they show aberrant play skills such as little symbolic play, ritualistic rigidity, and a preoccupation with specific parts of toys.

3. Restricted, repetitive, and stereotyped patterns of behavior and interests

Children with ASD can demonstrate atypical behaviors in a variety of areas, including peculiar mannerisms, unusual attachments to objects, obsessions, compulsions, self-injurious behaviors, and stereotypies. Children with autism ask the same question repeatedly, regardless of the reply that is given or engage in highly repetitive, perseverative play. They are also preoccupied with highly unusual special interests.

Many children with autism are preoccupied with consistency and prediction in their home and school environments or routines. Many of them demonstrate the classic behavior of lining up toys, videotapes, or other favored objects.

Diagnostic evaluation and screening

ASD can be reliably diagnosed in children as young as 2 years old and early intervention is beneficial[36]. The average age of diagnosis, however, is reported to be 3–6 years[37]. The American Academy of Pediatrics Council of Children with Disabilities recently published a set of guidelines on the identification and management of children with ASD[38].

According to the screening algorithm of ASD, the patient at a preventive care visit or at an extra visit for an autism-related concern should identify the risk factors, such as a sibling with ASD, parental concern for ASD, other caregiver concern, or pediatrician concern, and each risk factor has a score of 1[38].

If a patient has a score of 2 or higher, there should be parental education, comprehensive ASD evaluation, early intervention/early childhood education services, audiologic evaluation, and a scheduled follow-up visit. If a patient has a score of 1, the intervention choice will depend on the child's age. If the patient is at least 18 months old, he/she has to take the ASD-specific screening test. After the test, if the result is positive following

the two-score process and if the patient has no risk factor, ASD-specific screening will be recommended only if the visit is the 18 or 24-month preventive care visit.

1. Instruments for ASD screening

The Checklist for Autism in Toddlers, developed in Great Britain, is the most popular tool for screening 18- to 24-month-old children[39]. The Modified Checklist for Autism in Toddlers relies only on the parent's report[40]. The Screening Tool for Autism in Two-year-olds consists of interactive items administered by a clinician to a 24- to 35-month-old child[41].

2. Instruments for ASD diagnosis

The Childhood Autism Rating Scale is a clinician-rated diagnostic instrument for use with children older than 2 years[42].

The Autism Diagnostic Interview, Revised, a structured interview for parents, and the Autism Diagnostic Observation Schedule are considered as gold standards for the diagnosis of autism[43].

Neurologic evaluation

1. Neurologic examination

Most investigators report that a small proportion of children with autism have remarkable macrocephaly. The abnormalities in the neurologic examination may include hypotonia, which was observed in children with autism. Hand or finger stereotypical movement, body rocking, and unusual posturing are reported in 37%–95% of autistic individuals and these symptoms often manifest during the preschool years[36].

2. Evaluation of hearing

Many children diagnosed with autism are first described by their parents as acting "as if they are deaf." Audiologic evaluation or brainstem auditory-evoked potential testing should be performed in all children with autism so that if indicated, appropriate referrals can be made for aural habilitation[38].

3. Electroencephalography

There is no sufficient evidence for or against the use of routine electroencephalogram (EEG) screening in ASD patients. A recent review found that epileptiform EEG abnormalities were present in 10.3%–72.4% of the patients and subclinical abnormalities in 6.1%–31% of the patients[44].

4. Neuroimaging studies

Routine neuroimaging to evaluate a child with autism and macrocephaly is not warranted unless evidence of lateralizing signs is found in the neurologic examination.

5. Coexistent medical conditions

Children with ASD have several coexistent medical conditions such as gastrointestinal problems, sleep disturbance, epilepsy, and congenital blindness.

Treatment

1. Pharmacologic therapy

The goal of pharmacotherapy for children with autism is to alleviate the symptoms and specific behaviors. The target symptoms include sleep problems, anxiety, repetitive motor behaviors, obsessive-compulsive symptoms, impulsivity, depression, mood swings, agitation, hyperactivity, aggression, and self-injurious behavior.

Although there are no medications currently that directly impact cognitive impairment, controlling these symptoms should allow the child to maximize the benefits of educational and behavioral therapy that is directed more towards the core symptoms.

1) Neuroleptic agents

Risperidone and aripiprazole have been approved by the U.S. Federal Drug Administration for the treatment of irritability, such as aggression, self-injurious behavior, temper tantrums, and mood swings, in school-age children and adolescents with autistic disorders.

2) Serotonin reuptake inhibitors

The symptoms causing major impairment in autism, such as anxiety and repetitive and ritualized behaviors, can disrupt learning. Due to the effectiveness of serotonin reuptake inhibitors in alleviating the anxiety and obsessive-compulsive symptoms, and due to the finding that serotonin system abnormalities exist in individuals with autism[45], there has been a considerable surge in treating disruptive behaviors in autism with these agents.

3) Stimulants and drugs for treating hyperactivity

Hyperactivity is an important target symptom that can be potentially alleviated with psychostimulant medication[46].

4) Antiepileptic drugs

In open-label studies, levetiracetam and divalproex sodium appeared to be well tolerated and successful in alleviating repetitive behavior, impulsivity, and mood stability[47,48].

2. Educational and behavioral interventions

The prioritization of interventions should focus on six specific areas: functional spontaneous communication, social instruction delivered throughout the day in various settings, play skills, cognitive development, proactive approaches to problem

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behaviors, and functional academics.

Methods based on applied behavior analysis (ABA) for teaching skills and facilitating more appropriate and adaptive behaviors have been tested extensively for their effectiveness in children and adults with autism and other developmental disabilities[49]. In the most rigorously designed studies of intensive early intervention programs based on ABA, efficacy was demonstrated at the group level, but the response was variable.

Conclusions

For patients with developmental delays, especially patients with language delays, a differential diagnosis for ASD must be conducted when they visit a pediatric clinic. In ASD patients, appropriate behavioral therapy and rehabilitation treatment significantly affect the prognoses, and hence, it is important to make an early diagnosis and to treat the disorder at an early stage.

Therefore, pediatricians must be able to recognize the signs and symptoms of ASD and must be attentive to their presence in order to make an early diagnosis and be able to treat the disorder at an early stage.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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