Recent update of Autism Spectrum Disorders

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Abstract

In language-developmental delay patients, it is need to make differential diagnoses from autism spectrum disorders (ASDs), specific language impairment, and mental retardation. It is important that pediatricians be able to recognize the signs and symptoms of ASDs because, in many cases, language-developmental-delay patients are finally diagnosed with ASDs. Pediatricians have to play an important role in early recognition of ASDs, because they usually are the first point of contact for children with ASDs. A revision to ASDs was proposed in the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5), released May 2013. The autism spectrum describes a range of conditions classified as neurodevelopmental disorders in the fifth revision of the DSM-5. The new diagnosis encompasses previous diagnoses of autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder-not otherwise specified (PDD-NOS). An additional change to the DSM includes collapsing social and communication deficits into one domain. In ASDs patients, appropriate behavioral therapies and rehabilitation treatments significantly affect the prognoses, and as such, it is important to make an early diagnosis and treatment. Therefore, pediatricians be able to recognize the signs and symptoms of ASDs and must be attentive to it to be able to make an early diagnosis and treatment.

Key Words: Autism spectrum disorder, Developmental disorder, Genetics
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 and to provide parents with appropriate education programs. For children aged 9, 18, 30 months and 5 years, the Korean-Ages and stages questionnaires (K-ASQ) and Denver-II developmental assessments are used. When the infants or children show abnormal findings, they are referred to professional institutions for confirmatory diagnostic test of developmental delay. According to the report on the effects of the infant and children health screening, developmental delay was suspected in 0.6-2.5% of tested children, and 99% of these children were diagnosed with neurodevelopmental disorders. The final diagnoses included global developmental delay (50%), developmental language disorder (26%), cerebral palsy (10%), motor developmental delay (9%), and autistic disorders (4%)\(^1\).

Among the finally diagnosed developmental disorders, developmental language disorder was the second most common, and many autism spectrum disorders (ASDs) were also reported. In language delay patients, it is need to make differential diagnoses with ASDs, specific language impairment, and mental retardation. It is important that pediatricians be able to recognize the signs and symptoms of ASDs because, in many cases, language-developmental-delay patients are finally diagnosed with ASDs. Pediatricians have to play an important role in early recognition of ASDs, because they usually are the first point of contact for parents. The ASDs represent a wide continuum of associated cognitive and neurobehavioral deficits, including deficits in socialization and communication, with restricted and repetitive patterns of behaviors. ASDs are an organic neurodevelopmental disorders caused by genetic or neurobiological factors rather than by psychological or environmental ones. In DSM-5,
published in May 2013, revised ASDs diagnosis criteria were suggested and many genetic studies on the cause of ASDs have been actively conducted of late.

In this article, the most recently upgraded diagnosis criteria and the latest progression in the genetic studies on ASDs are 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 onset prior to 3 years of age and by a triad of behavioral signs and symptoms, including (a) abnormal development in the use of language, (b) lack of reciprocal social interaction and responsiveness, and (c) restricted, stereotypical, and ritualized patterns of interests and behaviors.\(^3\)

Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) [1994] and DSM-IV-TR (text revision) [2000] included five possible diagnoses under the PDD: autistic disorder, Asperger’s disorder, childhood disintegrative disorder, Rett’s syndrome, and PDD-not otherwise specified (NOS). A revision to ASDs was proposed in DSM-5, released May 2013.\(^4\)

The autism spectrum describes a range of conditions classified as neurodevelopmental disorders in the fifth revision of DSM. The new diagnosis encompasses the previous diagnoses of autistic disorder, Asperger’s disorder, childhood disintegrative disorder, and PDD-NOS.

It is thought that individuals with ASDs are best represented as a single diagnostic category because they showed 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 DSM-5 includes collapsing
social and communication deficits into one domain.

**Diagnostic Criteria**

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

**Epidemiology**

The prevalence of autism has dramatically increased, and it is recognized as one of the most common developmental disorders at present. For many years after autism was first described in the 1940s, its prevalence was considered two to four cases per 10,000 children.\(^5\) Based on the most recent parent-reported U.S. diagnostic survey, the prevalence of ASD was as high as 11 per 1,000.\(^6\) A number of factors contribute to this apparent increase. The diagnostic criteria have been broadened; the concept of autism is now defined as autistic disorder plus the broader ASDs, including Asperger’s syndrome and PDD-NOS. Also, there is now co-diagnosis with known medical disorders such as fragile X syndrome, Tourette’s syndrome (TS), and Down syndrome, and the growing public awareness among parents and teachers in developing countries has led to earlier diagnoses. Other factors include the increased availability of services\(^7\) and the ability to diagnose children at younger ages.\(^8\)
Pathophysiology and Etiology

1. Genetics

The known single-gene defects and the diagnosed medical conditions account for about 10% of the cases of autism.\textsuperscript{9} Between 21 and 50% of the boys with fragile X syndrome are on the autistic spectrum,\textsuperscript{10} and 0-6% of the autism populations have fragile X syndrome.\textsuperscript{11} The rates of ASD in tuberous sclerosis complex (TSC) most consistently range between 24 and 60%.\textsuperscript{10} The incidence of autistic individuals with TSC complex has been estimated to be between 0.4 and 4% in epidemiologic studies.\textsuperscript{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.\textsuperscript{13} Recently, it has been demonstrated that the CNV location and its functional relevance may play a more important role instead of the mean CNV number and size.

Indeed, two large datasets have been discovered of late: heterogeneous \textit{de novo} copy-number variants collectively affecting several loci and presumably accounting for 5-8% of the cases of simplex forms of ASD.\textsuperscript{14} The network-based functional analysis of these rare CNVs confirms the involvement of these loci in synapse development, axon targeting, and neuron motility.\textsuperscript{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.\textsuperscript{16} At the extracellular level, postsynaptic neuroligins interact with presynaptic or neurexins stimulating the formation of the presynaptic bouton\textsuperscript{17}; at the intracellular level, neuroligins associate with postsynaptic scaffolding proteins such as SHANK3.\textsuperscript{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 possibly causative of autism.

Three members of the SHANK gene family (SHANK1, SHANK2, and SHANK3), which encode the scaffolding proteins required for the proper formation and function of neuronal synapses. Recently, SHANK2 mutations have also been reported both in ASD and in 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 correct brain function and development: loss of MeCP2 has been shown to delay neuronal maturation and synaptogenesis, and MECP2 \textit{de novo} loss-of-function mutations cause Rett syndrome in approximately 70\% of the affected females while they are generally lethal in males.\(^{20}\)

Children with idiopathic autism often display minor facial dysmorphisms\(^{21}\) and abnormal head/body growth rates.\(^{22}\) Macrocephaly is demonstrated in approximately 20\% of autistic children.\(^{22}\) The Hox genes play a crucial role during embryonic patterning and organogenesis.

The phosphatase and tensin homolog (PTEN) gene, located on chromosome 10q23, harbors mutations associated with a broad spectrum of disorders, including Cowden syndrome (CS), 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 mTOR. Recently, a balanced translocation disrupting the EIF4E locus was found in a boy with ASD displaying 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.\(^{27}\) Only in rare instances do mutations in mitochondrial DNA (mtDNA) or in nuclear DNA (nDNA) heavily involved in the mitochondrial function explain the disease. Children with mitochondrial disease thus represent a small percentage (<1%) of all autistic patients. Truly mitochondrial ASD forms are indeed 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.\(^{29}\) In the epigenetic theory, environmental factors may modulate the already-existing genetic factors responsible for the manifestation of ASDs in individual children. The increasing age of mothers, independently and with the increasing age of fathers, is a risk factor of ASD.\(^{30}\)

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 autistic children had an above-average brain volume at 2-4 years old, and 37% have developmental macrocephaly, defined as a brain volume exceeding 2 standard deviations above the normal mean for age.\(^{32}\) This finding reveals an ongoing postnatal
process that primarily affects the interhemispheric and cortical connections.

The results of recent functional MRI studies (fMRI) point to changes in the activation and synchronization of cortical networks. The functional connectivity is lowered, leading to deficits in language, social cognition, motor planning, and perception.\textsuperscript{33}

4. Neuropathology

Kemper and Bauman\textsuperscript{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 non-verbal 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 (IQ) tests.

1. Impairment of Social Interactions

ASD infants may or may not cuddle, or may even stiffen when held, and often do not look or smile when making a social approach. 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 seem to among the primary
distinguishing characteristics of ASD children.\footnote{35}

Autistic children 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 they are described as “quiet babies.” Moreover, they cannot compensate for this with facial expressions or gestures. A hallmark of autistic speech is immediate or delayed echolalia. Some autistic children do not appropriately use toys, animals, or dolls in pretend play. Also, they show aberrant play skills such as little symbolic play, ritualistic rigidity, and 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. Autistic children ask the same question repeatedly, regardless of the reply that is given, or engage in highly repetitive, perseverative play. They are also preoccupied with special interests that are highly unusual.

Many autistic children are so 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.\textsuperscript{36} The average age of diagnosis, however, is reported to be 3-6 years.\textsuperscript{37} American Academy of Pediatrics Council of Children with Disabilities recently published a set of guidelines\textsuperscript{38} on the identification and management of children with ASD. According to the screening algorithm of ASD\textsuperscript{38}, 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.

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 choice will depend on the child’s age. If the patient is at least 18 months old, he 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 indicated only if the visit is the 18\textsuperscript{th}- or 24\textsuperscript{th}-month preventive-care visit.

1. **Instruments for ASD Screening**

Checklist for Autism in Toddlers (CHAT)\textsuperscript{39}, developed in Great Britain, is the most popular tool for screening 18- to 24-month-old children. Modified Checklist for Autism in Toddlers (M-CHAT)\textsuperscript{40} relies only on the parent’s report. Screening Tool for Autism in Two-year-olds (STAT)\textsuperscript{41} consists of interactive items administered by a clinician to a 24- to 35-month-old child.

2. **Instruments for ASD Diagnosis**

Childhood Autism Rating Scale (CARS) is a clinician-rated diagnostic instrument for use with children older than 2 years\textsuperscript{42}
Autism Diagnostic Interview – Revised (ADI-R), a structured parent interview, and Autism Diagnostic Observation Schedule (ADOS), are considered the gold standards for the diagnosis of autism.\textsuperscript{43}

**Neurologic Evaluation**

1. **Neurologic Examination**

Most investigators report that a small proportion of autistic children have remarkable macrocephaly. The abnormalities in the neurologic examination may include hypotonia, which was observed in autistic children. Hand or finger stereotypical movement, body rocking, and unusual posturing are reported in 37-95\% of individuals, and they are often manifested during the preschool years.\textsuperscript{44}

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.\textsuperscript{45}

3. **Electroencephalography**

There is no sufficient evidence for or against the use of routine screening EEGs 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\%.\textsuperscript{46}

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.
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 the sleep problems, anxiety, repetitive motor behaviors, obsessive-compulsive symptoms, impulsivity, depression, mood swings, agitation, hyperactivity, aggression, and self-injurious behavior.

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

1) Neuroleptic agents

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

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 of serotonin system abnormalities in individuals with autism\textsuperscript{47}, there has been considerable interest 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.\textsuperscript{48}

4) **Antiepileptic drugs**

In open-label studies, levetiracetam\textsuperscript{49} and divalproex sodium\textsuperscript{50} appeared to be well tolerated and to alleviate repetitive behavior, impulsivity, and mood stability.

2. **Educational and Behavioral Interventions**

The prioritization of intervention 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 behaviors, and functional academics. Methods based on applied behavior analysis for teaching skills and facilitating more appropriate and adaptive behaviors have been extensively tested for their effectiveness in children and adults with autism and other developmental disabilities.\textsuperscript{52} In the most rigorously designed studies of intensive early intervention programs based on applied behavior analysis (ABA), efficacy was demonstrated at the group level, but the response was variable.

**Conclusion**

For developmental-delay patients, especially language delay patients, who were visited at a pediatric clinic, differential diagnosis with autism spectrum disorder (ASD) must be
conducted. In ASD patients, appropriate behavioral therapy and rehabilitation treatment significantly affect the prognoses, and as such, it is important to make an early diagnosis and to treat the disorder at its early stage.

Therefore, pediatricians must be able to recognize the signs and symptoms of ASD and must be attentive to it to be able to make an early diagnosis and to be able to treat the disorder at its early stage.
Conflict of Interest

No potential conflict of interest relevant to this article was reported.
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Table 1. DSM-V diagnostic criteria for autism spectrum disorders

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<thead>
<tr>
<th>DSM-IV</th>
<th>DSM-5</th>
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<tr>
<td>(1) Social impairment</td>
<td>(1) Deficits in social communication</td>
</tr>
<tr>
<td>(2) Speech/Communication deficits and language delay</td>
<td>(2) Restricted, repetitive patterns of behavior, interests</td>
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<tr>
<td>(3) Repetitive behaviors and restricted interests</td>
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### Table 2. Categories of autism spectrum disorders

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<tr>
<th>DSM-IV</th>
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<tr>
<td>Pervasive Developmental Disorders (PDD)</td>
<td>Autism Spectrum Disorder</td>
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<td>(1) Level 3</td>
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<td>: Requiring very substantial support</td>
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<tr>
<td>(2) Asperger’s disorder</td>
<td>(2) Level 2</td>
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<td></td>
<td>: Requiring substantial support</td>
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<tr>
<td>(3) Rett’s syndrome</td>
<td>(3) Level 3</td>
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<td></td>
<td>: Requiring substantial support</td>
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<tr>
<td>(4) Childhood disintegrative disorder</td>
<td></td>
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<tr>
<td>(5) PDD-not otherwise specified (NOS)</td>
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