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Korean Clinical Guideline for Autism Spectrum Disorder - Clinical Features, Course, Epidemiology, and Cause

Jun-Won Hwang[1] and Jeong-Seop Lee[2]

[1]Department of Psychiatry, Kangwon National University Hospital, Kangwon National University School of Medicine, Chuncheon, Korea
[2]Department of Psychiatry, Inha University Hospital, Inha University School of Medicine, Incheon, Korea

Autism spectrum disorder (ASD) is a heterogeneous developmental disorder characterized by impairments in two core areas: 1) social communication and interaction and 2) restricted and repetitive patterns of behaviors and interests. In general, ASD is known to be a lifelong disorder. Follow-up studies from childhood to adulthood have reported that the severity of the key symptoms ASD decreases over time. However, chronic health problems including mental health occur in many patients with ASD. The prevalence of ASD has increased from around 0.04% in the 1970s to 2.8% at present. The average age of diagnosis in developed countries is 38−120 months of age. Recent evidence suggests that biological factors which include genetic, congenital, immunological, neuroanatomical, biochemical, and environmental ones are important in causing autism. Until now, early signs and various risk factors of ASD have been suggested.

Keywords: Autism spectrum disorder; Associated features; Disease progression; Epidemiology; Cause.

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Address for correspondence: Jeong-Seop Lee, Department of Psychiatry, Inha University Hospital, Inha University School of Medicine, 27 Inhang-ro, Jung-gu, Incheon 22332, Korea
Tel: +82-32-890-3477, Fax: +82-32-890-3580, E-mail: soulfree@inha.ac.kr

INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous developmental disorder characterized by impairments in two core areas: 1) social communication and interaction and 2) restricted and repetitive patterns of behaviors and interests. Importantly, the two main classification systems in the psychiatric taxonomy of diagnosis (Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition [DSM-5]: American Psychiatric Association and International Classification of Diseases 11th Revision [ICD-11]: World Health Organization [WHO]) specified that ASD is not a psychotic disorder but a neurodevelopmental disorder. In other words, as the key symptoms generally appear from infancy, the child's social development, communication, learning and adaptive development, and overall functioning are negatively affected. The term spectrum refers to a wide range of symptoms as well as skills and disabilities at different levels that can be manifested in people with ASD. Therefore, ASD has been considered a quantitative concept rather than a categorical viewpoint that determines whether patients with ASD are disabled [1,2].

The concept of this disorder has been constantly changing since Kanner [3] reported 11 cases in 1943, which he termed infantile autism. By 1980, autism was officially recognized as a diagnosis in DSM-III [4]. The United States DSM-IV, published in 1994, used the pervasive developmental disorder (PDD) diagnostic category and included five diagnostic subtypes: autistic disorder, Asperger's syndrome, Rett's disorder, childhood disintegrative disorder, and PDD not otherwise specified. In the DSM-5 published in 2013, the diagnostic category of this disorder was integrated into ASD based on the data suggesting that the subtype classification was not clinically significant (Supplementary Material 1 in the online-only Data Supplement). This reflects the current scientific consensus that ASD can be integrated into a single form of spectrum despite the varying degrees of symptoms in the two fundamental areas [4].

In contrast, the ASD diagnostic criteria of ICD-11 published by the WHO in 2018 specified that defects in the abovementioned two fundamental areas should be severe enough to affect an individual, family, society, education, occupation, or other important functional areas [5]. Such disorders are generally observed in all environments, and although the severity of symptoms may vary depending on the situation, the symptoms should interfere with the person's general ability to function to be considered ASD symptoms. In addition, unlike DSM-5, which only specified the severity of disability,

ICD-11 suggested subcategories for various levels of intellectual and linguistic functions (Supplementary Material 2 in the online-only Data Supplement). ICD-11 came into effect on January 1, 2022, but the 8th revision of the Korea Standard Classification of Diseases is still based on ICD-10 [6].

CLINICAL FEATURES

Deficits in social communication and social interaction

Deficits in social interaction

A wide variety of behavioral patterns, such as attempting inappropriate social approaches and completely failing to initiate social interactions, may be observed in patients with ASD. Owing to the influence of such behavioral patterns, it may be difficult to establish social relationships appropriate for the developmental age with individuals other than parents, and such patients may not be able to interact emotionally. Moreover, when others try to interact with them, they have no interest or show inappropriate, superficial, and restricted reactions. Furthermore, such patients cannot behave appropriately in diverse social situations. During infancy, they rarely show a social smile, barely make eye contact, or maintain unsteady eye contact. In many situations, they do not present with shyness or separation anxiety. The playing characteristics of children with ASD are nonsocial; in particular, such children are unable to do role play or engage in imaginary play that requires cooperation, and there is a lack of symbolism when they play [2,4].

Deficits in social communication

The verbal communication of patients with ASD is poor, and such patients rarely use nonverbal communication. Moreover, their language development is delayed, and even when their language is developed, it remains abnormal. In addition, even with acquired language skills, they do not try to use these skills for communication. Their speaking pitch is monotonous, with unusual speech intonation; moreover, inappropriate patterns are observed in their speech rhyme. Children with ASD and relatively developed language skills usually demonstrate one-way conversation because they do not consider the other person's reaction; hence, it is not easy to continue a conversation with them. Commonly used gestures are absent in such patients, and joint attention, which is important in nonverbal communication, is also lacking. Therefore, such patients do not voluntarily attract the attention of others and hardly react to what others point out [2,4].

Restricted, repetitive patterns of behaviors, interests, or activities

Stereotyped and repetitive movements and speech

In patients with ASD, the most common movements are finger flicking or crossing, spinning, tiptoeing, and hand clapping. In cases where behaviors are presented in verbal form, such patients typically use unusual phrases repeatedly, echo words that mimic words heard in the past or recently, and use newly created neologisms [2,4].

Persistence for uniformity and resistance to change

Patients with ASD repeat the same behavior and are very resistant to even small changes. They tend to insist on the same thing and do not accept new surroundings or experiences. They stick to their own everyday rules by insisting on the same style of dress, walking the same path, or only eating certain foods. Moreover, they demonstrate a continuous obsession with certain objects [2,4].

Restrictive and fixed attention and interests

The object of interest is very restrictive and fixed in patients with ASD, and both intensity and focus are abnormal in such patients. Moreover, these patients tend to have interests in unusual and nonsocial topics, such as the subway, bathroom, guns, dinosaurs, etc., and these interests remain fixed, without change with excess intensity from time to time [2,4].

Abnormal reactions to the senses

Although there are cases of excessive pain or temperature insensitivity, it is commonly observed that such patients loathe certain sounds (e.g., the sound of a vacuum cleaner, the sound of toilet flushing, etc.). They sometimes repeatedly smell a peculiar odor, or in some cases, they are excessively attracted to light movements [2,4].

COURSE AND PROGNOSIS

In general, ASD is known to be a lifelong disorder. However, follow-up studies from childhood to adulthood have reported that the severity of the key symptoms ASD decreases over time, and in few cases, the ASD diagnostic criteria are no longer met [7]. In many cases, it has been reported that communication and social interaction skills in people with ASD improve significantly as they get older. Language development and average nonverbal intelligence quotient (IQ) have been suggested as the most reliable predictive factors for a positive prognosis [8,9].

Despite several positive study results, continued professional development should be offered to most patients with ASD who

present with more than moderate cognitive impairment, particularly those without verbal communication skills. In addition, support is needed for their employment and activities of daily living in adulthood. This is because the prognosis in adulthood is generally poor even with an above-average IQ [10]. Moreover, even in developed countries, there are few opportunities for higher education or employment for these patients, and <30% of people with ASD work full-time. Most patients with ASD respond to family or government support. Although they are autistic with high intellectual capacity (e.g., IQ >70), adequate social support should be provided to enable them to lead independent lives in regular schools, colleges, and the workplace as well as to be fully integrated into society; notably, the prognosis of such patients depends on these factors [11,12].

Mental health problems occur in many patients with ASD. Moreover, physical symptoms and chronic health issues are more common in such patients than in the general population, and recent studies have reported a risk of premature death in such patients. Notably, premature death rates are particularly high in ASD patients with intellectual disabilities and epilepsy. Importantly, suicide is a key cause of premature death in ASD patients with above-average IQs [13-15].

Relatively little is known about the lives of older people with autism (e.g., those aged ≥60 years). Some studies have reported that older people with autism may experience less deterioration in mental health and overall quality of life than the general older population and that these people may be at a lower risk for Alzheimer's disease and dementia [16].

EPIDEMIOLOGY

Prevalence and associated features

The prevalence of ASD has increased from around 0.04% in the 1970s to 2.8% currently, which could be attributed to differences in methodology, diverse sampling processes, and inconsistent case definitions and diagnostic criteria [16,17]. Recently, the prevalence of ASD for ages 3–21 years in United States ranged from 1.5% to 2.3% [18]. In addition, the prevalence for ASD among 5–18-year olds in Europe was estimated at 0.8% based on register-based studies and 1.4% based on population-based studies [19]. In Korea, estimated prevalence of ASD according to DSM-5 was 2.20% [20]. Given the lack of data from low and middle income countries, the WHO estimated the global prevalence of autism to be approximately 1% in 2012 [21].

Previous studies have shown that ASD is 3–4 times more common in males than females in hospitalized patients, and female patients with ASD have more severe intellectual disability [18]. With the exception of Rett syndrome, other PDDs are also more common in males. In ASD, severe to profound intellectual disability is reported in approximately 50% of cases and mild to moderate intellectual disability is found in approximately 30% of cases [22].

The risk factors for ASD are presented in Table 1.

Early detection

While parents usually concern about their child's development at around 18–24 months of age, the average age of diagnosis in developed countries is 38–120 months [23]. In underdeveloped countries or population groups with no health insurance or poor access to healthcare, the age of diagnosis can be much later.

In addition to delays in babbling/speech, early symptoms that parents worry about include delays in pointing or gesturing, and responding to their name, as well as poor eye contact [24]. Difficulties in peer interaction or abnormal repetitive behaviors may not be evident during the first two to three years of life, so it should not be ruled out that a child may have ASD just because of the absence of these features during infancy.

The Centers for Disease Control and Prevention (CDC) webpage lists the following "red flags" for early signs of ASD (Table 2) [25].

The American Academy of Pediatrics (AAP) recommends universal screening for ASD at 18 and 24 months, and regular developmental monitoring at 9, 18, and 30 months during well-child visits [26]. However, the United States Preventive Services Task Force has concluded that there was insufficient

Table 1. The risk factors for autism spectrum disorder

Siblings of confirmed cases
Babies of older or very young mothers and older fathers
A history of suboptimal prenatal or perinatal development (e.g., medication use during pregnancy, hypertension, infection, and maternal obesity)
Various genetic disorders (e.g., Rett's syndrome, Cohen's syndrome, Cornelia de Lange syndrome, tuberous sclerosis, Angelman's syndrome, CHARGE syndrome, fragile X syndrome, neurofibromatosis type 1, Down's syndrome, Noonan's syndrome, Williams' syndrome, and 22q11.2 deletion syndrome)
Various psychiatric disorders, especially obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), anxiety disorders, and mood disorders

Table 2. Early signs of autism spectrum disorder

Does not respond to his/her name by 12 months of age
Does not point at objects in order to show interest by 14 months of age (e.g., not pointing at an airplane flying by)
Does not engage in pretend play of "feeding a doll with food" by 18 months of age
Avoids eye contact and wants to be alone
Difficulty in understanding other people's emotions or expressing their own emotions
Delayed abilities in speech and language
Echolalia
Giving unrelated answers to questions
Being upset when minor changes occur
Obsessive interests
Flapping hands, rocking back and forth, or spinning in circles
Unusual reactions to sound, smell, taste, appearance, or feel of objects

evidences in order to recommend the universal screening for children "who have not been identified by parents, guardians, or other health care professionals as having concerns about ASD" and that more research would be needed in terms of potential benefits of screening at this time [27].

There is no single test or measure that will be recommended for early detection of ASD [28], and multiple screening tools that are commonly used can be employed. Although most screening tools have higher sensitivity than specificity, from a public health perspective, this can be considered a positive asset because it identifies cases that require earlier developmental support.

CAUSE

For many years after Kanner specified "refrigerator mothers" as the cause of autism, it was believed that this was one of the causes of autism. However, recent evidence suggests that biological factors are important in causing autism.

Genetic factors

Through family studies, twin studies, and chromosomal studies, genetic factors have been found to be very important. The risk of siblings of an autism patient becoming autistic is about 2.2%, and the risk of developing PDDs, excluding autism, is about 3.6% [29-32]. In other words, the risk of siblings of an autism patient being affected by PDDs is estimated to be about 5%−6%. In contrast, the risk of ASD in second- and third-degree relatives of patients with ASD is about 0.18% and 0.12%, respectively [29,33,34]. In twin studies, monozygotic twins show a higher concordance rate than dizygotic twins [35-38].

The exact genetic model of ASD has not yet been identified. This is thought to be due to various factors such as expressivity, penetrance, and genetic heterogeneity [39]. Although genome-wide association studies (GWAS) have found several potential genes for ASD, the heterogeneity of ASD limits the ability to identify potential variants [40-42]. Recently, de novo rare variants have been investigated as these would contribute genetic susceptibility to ASD.

Congenital factors

A variety of neurological disorders have been associated with autism symptoms, including severe cerebral hemorrhage, cerebral palsy, tuberous sclerosis, giant cell astrocytoma, meningoencephalitis, congenital rubella, toxoplasmosis, lead poisoning, and epilepsy. It has also been argued that prenatal or perinatal brain injury is the biological cause of autism symptoms that appear after birth, whereas postnatal brain infection or damage is the cause of autism disorders that appear after normal development. A history of prenatal, perinatal, and postnatal complications has been reported to be higher in patients with ASD, including maternal age, first child, fourth or last-born child, hemorrhage after three months of first pregnancy, medication use, meconium in amniotic fluid, low birth weight, congenital malformations, etc. [43,44]. However, it is unlikely that ASD is caused by any one obstetric factor, and the high rate of obstetric complications is probably due to genetic factors or the interaction between genetic and the environment ones [44-46].

Immunological factors

Since Chess reported a higher incidence of autism in those with congenital rubella, Deykin and MacMahon [47] have reported an association with prenatal influenza or rubella in 5% of autism cases. In addition, decreased activity of natural killer cells and inhibition of giant cell migration have been reported in autism [48,49]. Activation of neuroglial cells and the natural immune system has also been reported in the brain tissue and cerebrospinal fluid of subjects with ASD, suggesting that abnormalities in neuroimmune system occur in the brain of those with ASD [50].

Neuroanatomical factors

In postmortem autopsies, neuropathology in ASD is reported to be present before the second trimester, with anatomical abnormalities mainly in the frontal-temporal-parietal cortex, limbic system, and cerebellum, but the findings are inconsistent due to differences in the inclusion or diagnostic criteria used in the studies and major variables including age and intelligence of the participants [51]. Later studies have reported gray matter changes in the central region of the brainstem, increased volume of the caudate nucleus, and decreased brain volume [52-54].

Social comprehension skills (specifically theory of mind tasks) are associated with the prefrontal gyrus, superior temporal sulcus, amygdala, ventral and medial temporal lobes, and cerebellum, and it has been reported that all of the above-listed regions are not activated and have significantly reduced functional connectivity when performing theory of mind tasks in adults with ASD [55,56].

Biochemical factors

Many studies have reported hyper-serotonemia in one-third of those with ASD, but there were also reports that cerebrospinal fluid concentrations of the metabolite 5-HIAA were no differences in children with ASD from control subjects without neurological impairment [39]. In a series of studies, concentrations of homovanillic acid (HVA), a metabolite of dopamine, were not different in children with autism compared to other diagnostic groups, and higher cerebrospinal fluid HVA concentrations were associated with more severe impairment [57,58]. Abnormalities in norepinephrine and endogenous opioids have been suggested to be associated with autism. However, but there is a lack of consistency among studies and the causal mechanisms are unclear [59].

Environmental factors

Pre- and peri-natal factors, as well as maternal diet and lifestyle factors, have been implicated as environmental factors [60]. In particular, maternal age of 40 years or older and paternal age of 50 years or older, pregnancy intervals of 24 months or less, nonspecific factors such as maternal weight gain, hypertension, and metabolic disease, as well as more specific factors including maternal hospitalization for infectious diseases and family history of autoimmune disease, are known to moderately increase the risk of ASD and developmental delay [61-63].

Prenatal valproate exposure is known to increase the risk of ASD, whereas selective serotonin reuptake inhibitor (SSRI) and other antidepressant exposure has been suggested to not increase the risk, contrary to past concerns [64,65]. Preterm birth at 32 weeks or less, low birth weight of 1500 g or less, and low or high birth weight at antenatal period have also been associated with an increased risk of ASD, but causality is unclear [66].

Prenatal supplementation of folate has been shown to reduce the risk of ASD and general developmental disorders, and associations have been found between some air pollutants and maternal stress during pregnancy [67]. Although it has been investigated several times, the association between vaccination and ASD has not been proven [68].

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.5765/jkacap.230040.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Conflicts of Interest

Jun-Won Hwang, a contributing editor of the *Journal of the Korean Academy of Child and Adolescent Psychiatry*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Jun-Won Hwang, Jeong-Seop Lee.

ORCID iDs

Jun-Won Hwang https://orcid.org/0000-0001-5407-8514
Jeong-Seop Lee https://orcid.org/0000-0001-5585-0334

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