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Review

Tic & Tourette Syndrome and Motor Disorders

Tae Won Park[1,2], Juhyun Park[3]

[1]Department of Psychiatry, Chonbuk National University Medical School, Jeonju, Korea
[2]Research Institute of Clinical Medicine of Chonbuk National University-Biomedical Research Institute of Chonbuk National University Hospital, Jeonju, Korea
[3]College of Medicine, Seoul National University, Seoul, Korea

Motor disorders in childhood include tic disorder, developmental coordination disorder, and stereotypic movement disorder. A tic is a sudden, rapid, repetitive and nonrhythmic movement (motor tics) or phonic production (phonic or vocal tics) that can occur at any part of the body. Developmental coordination disorder (DCD) is characterized by marked impairment in the acquisition and performance of motor skills. Stereotypic movement disorder is a common childhood disorder which repetitive, hard to control, aimless motor activity interrupts everyday life or causes self-infliction of a child. Despite increased attention and the growing scientific knowledge about motor disorders, there are limitations in our understanding and knowledge about the pathogenesis and the management of the disorders. Motor disorders can itself be the primary diagnosis, or can be secondarily diagnosed caused by other disorders, and accompany many neuropsychiatric disorders such as autism and attention deficit hyperactivity disorder (ADHD), which in turn impairs proper learning and socializing of the children with motor disorders. Therefore comprehensive medical history taking, continuous observation of the changes in symptoms, and systematic assessment considering the child's developmental stage and current adaptive capacity are needed. Behavioral therapy and pharmacological therapy are the two most often mentioned treatments of motor disorders.

Key Words: Child; Adolescent; Tic Disorders; Motor Skills Disorders; Stereotypic Movement Disorder

Correspondence to: Tae Won Park
Department of Psychiatry, Chonbuk National University Medical School, 567 Baekje-daero, deokjin-gu, Jeonju 54896, Korea
Tel: +82-63-250-2028
Fax: +82-63-275-3157
E-mail: ptaewon@jbnu.ac.kr

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INTRODUCTION

Motor disorder refers to neuropsychiatric disorders such as abnormal movements, meaningless repetitive movements, and impairment in acquisition and performance of motor skills. Motor disorder was included as a sub-category of neurodevelopmental disorder chapter in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) [1]. DSM-5's motor disorders include tic disorders (Tourette's disorder, persistent motor or vocal tic disorder, provisional tic disorder, other specified tic disorder, and unspecified tic disorder), developmental coordination disorder, and stereotypic movement disorder. This review overviews and summarizes current knowledge on the motor disorder's cause, diagnosis, and treatment.

TIC DISORDERS

A tic is a sudden, rapid, repetitive and nonrhythmic movement (motor tics) or phonic production (phonic or vocal tics) that can occur at any part of the body. Tourette's syndrome (TS) is a severe form of tic disorder, characterized by multiple motor and vocal tics that persist for at least 1 year. Tic disorder accompanies various neuropsychiatric disorders while chronic and repeatedly waxing and waning, which in turn impairs proper learning and socializing in children and adolescents. In some cases, these impairments extend to adulthood, thus having detrimental effects on social life of the patients.

Tic disorder was first included in DSM-III (DSM, 3rd edition) as a diagnosis [2]. In DSM-IV (DSM, 4th edition), the age of dis-

ease occurrence limit of tic disorder was lowered to 18 from 21 [3], and diagnosis was only limited to cases which affected normal life. However, in DSM-IV-TR (DSM, 4th edition, text revision), the boundary of diagnosis was expanded and also included cases in which normal life was not affected [4]. In DSM-5 (DSM, 5th edition), the term chronic tic disorder was changed to persistent tic disorder and transient tic disorder was changed to provisional tic disorder [1].

1. Epidemiology

TS was considered rare in the past but in recent studies it was shown that the incidence rate in childhood is 1% and 3-5 times more likely to occur in males [5,6]. Persistent tic disorder occurs 2-4 times more often than TS and about 20% to 30% of schoolchildren experience at least one transient tic [7]. TS occurs in all races with variation among groups [6]. Different studies report substantially different prevalence rates, which is probably caused by inconsistent research subjects and diagnostic criteria.

2. Risk factors

From twin and family studies, there is plenty of evidence that point to inheritability of TS and persistent tic disorder. In the case of TS, concordance in homozygous twins is 53-56%, and 8% in heterozygous twins and when persistent tic disorder is also taken into account, concordance rate increases to 77% in homozygous twins and to 23% in heterozygous twins [8]. The fact that concordance does not reach 100% tells us that environmental factors do exist. In familial hereditary studies, prevalence rates in biological families are high regardless of region or race. Prevalence of tic in first-degree relatives of TS or persistent tic disorder patients is 25-41% [9,10], while in the general population it is 1-1.8%. Moreover, in familial studies of TS, it has been shown that prevalence of obsessive compulsive disorder (OCD) is also higher than the general population besides tic: this pattern is more prominent in females [9].

Although less mentioned than genetic factors as causes of tic disorder, environmental factors do have an effect on tic. However, too many limitations exist in studying them. Examples of environmental factors include pregnancy or perinatal problems, various drugs, general medical conditions, immunological factors such as autoimmunity, and other life events [11].

3. Pathogenesis

As in OCD, many held the cortico-striato-thalamo-cortical (CSTC) pathway's malfunction responsible for tic disorder [11]. CSTC pathways that originate from the motor cortex and dorsolateral cortex are thought to have the most effect. This CSTC pathway hypothesis in tic disorder is backed up by studies such as neuroimaging studies [12,13]. The basal ganglia encompass a network of these brain structures. CSTC pathway malfunction is thought to be caused by complex interaction between parts of the pathway, which in turn causes motor symptoms, premonitory urges, and emotional symptoms [14]. Disturbances of diverse neurotransmitter systems involved in this circuitry have been thought to play an important role in the pathogenesis of TS, including abnormalities in the dopamine, gamma-aminobutyric acid (GABA), glutamate, and serotonin systems [15]. Dopamine receptor supersensitivity has been thought to be present in TS. The hypothesis was partly supported by the findings, such as reduced level of homovanillic acid in the cerebrospinal fluid of patients and the relieving effects of dopamine receptor antagonist [16]. Increased binding to presynaptic dopamine transporter site in postmortem striatum from cadavers was also observed [17].

Various changes in brain regional volume have also been reported in neuroimaging studies of TS, although the results have been inconsistent. Reduced volume of grey matter in the frontal lobe and the loss of normal asymmetry were reported [18]. Caudate volumes have been correlated inversely with the severity of tics [19].

4. Clinical characteristics

Tics are defined as sudden, rapid, repetitive and nonrhythmic movements or vocalization and sometimes mimic normal behavior [20]. Tics may be further classified as simple or complex tics. Simple motor tics involve isolated muscle groups and manifest in a single anatomical location, characterized by fast and meaningless muscle movements. Examples of simple motor tics include eye blinking, nose twitching, and shoulder shrugging. By contrast, complex motor tics involve multiple muscle groups. They are slower and more protracted movements or behaviors and appear more purposeful [21]. Examples of complex motor tics include repetitive touching objects, jumping, and back arching. Simple vocal tics consist of inarticulate sounds or noises, such as throat clearing, coughing, and sniffing. Complex vocal tics include intelligible syllables, words, and phrases. The coprolalia may be the most recognizable and distressing symptoms of TS. Recent international studies reported that coprolalia occurred at some point in the course of disease in 19% of males and 15% of females [22].

Premonitory urge which is experienced by the majority of tic patients is known to be relatively rare before the age of 10 and occurs in 37% of child patients [23]. Paresthesia (numbness, itchiness, tension, etc.) at certain parts of the body or general physical discomfort or tension often come before tics. Shoulder girdle, throat, hand, center of gastrointestinal tract, fore part of thigh, and instep of foot are body parts that premonitory urge is most experienced [24].

5. Differential diagnosis and comorbid disorders

Other motor symptoms that need discrimination from tic include chorea, dystonia, athetoid movement, dyskinesia, hemiballism, hemifacial spasm, stereotypy, and compulsive behavior [25]. Still other diseases that need discrimination are motor symptoms caused by various factors. Abnormal movement disorders that are caused by drugs such as antipsychotic drugs also require discrimination. There are also abnormal body movements accompanied by physical illnesses such as Huntington's disease, Parkinson's disease, stroke, Sydenham's chorea, Wilson's disease, and Lesch-Nyhan syndrome. Age of onset, history of general tic or facial tic, degree of control of abnormal movements, changes in motor symptoms, and accompaniment of premonitory urge must be taken into account when discriminating.

Premonitory urge makes complex tic and OCD difficult to discriminate. This stems from the fact that premonitory urge experienced by complex tic patients closely resembles thought or urge experienced by OCD patients. However, cognitive phenomena and physiological symptoms of anxiety may proceed in OCD but not in TS [26].

Obsessive-compulsive symptoms have been reported in 11-80% of TS patients [27], and it usually occurs simultaneously with or before tics. The onset of obsessive-compulsive symptoms is mostly at the end of childhood or the start of adolescence, the period at which Tourette symptoms decreases [11]. Obsessive-compulsive symptoms often seen in tic patients include compulsion on symmetry and repeated counting, arranging, trimming comprehensively called the "just right phenomenon." [28].

Attention deficit hyperactivity disorder (ADHD) is the most common comorbid diagnosis in children and adolescents with tic disorders [29], and often occurs before tic symptoms emerge in TS [11]. Behavioral disorders often accompanied by tic disorder patients include offensive behavior, temper tantrum, oppositional behavior, and impaired social interaction. Moreover, TS is often accompanied by autism spectrum disorder, and vice versa. The mentioned disorders are often accompanied by but not regarded as core symptoms of TS. These behavioral disorders are probably more related to accompanied ADHD rather than TS itself, but not so easy to catch because of ascertainment bias.

Besides behavioral disorders, anxiety disorders, depressive disorders, migraine, and sleep disorders are often accompanied in children with tics.

6. Treatment

1) General principle

Before describing available treatments, it is important to emphasize the importance of clinical observation: knowing changes in symptoms and patients' coping strategies can be very helpful. Observations can be recorded in a form of a diary: changes in the most obvious tics and the child's strategies in countering such changes can be recorded daily. Although observation can be helpful in grasping symptoms and efficiently controlling them, the feeling of being observed itself in a child can actually backfire, aggravating tics, by making him recall the symptoms more often, so caution must be taken.

Moreover, psychoeducation that gives the patient and his family accurate information to understand problems is absolutely essential and has been described as the cornerstone for all other intervention [30]. This can correctly educate the patient and the guardian about the cause of the tic and the fundamentals of its symptoms. This may lower unnecessary terror and prevent recrimination among family members.

It is also very important to evaluate secondary causes and assessing psychosocial factors and comorbid psychiatric conditions [31,32]. Behavioral therapy and pharmacological therapy are two most often mentioned treatments of childhood tic, and recently transcranial magnetic stimulation (TMS) is drawing more attention, although its effectiveness remains to be seen.

2) Behavioral therapy

There are increasing reports that a variety of recently developed behavioral therapies mitigate severity and frequency of tics. Various behavioral techniques have been developed, but habit reversal training (HRT) and exposure and response prevention (ERP) are getting the most spotlight [33].

Habit reversal training was reported to be effective in open studies, and recently it was reported to be significantly more effective

in randomized control studies performed on children than in widely-known supportive therapy [34]. In HRT, competing response, in which tension is applied to muscles not related to tic, which leads to habituation of unpleasant feelings such as premonitory urge, is used. Competing response may be applied for several minutes. In the case of motor tics, isometric tension is applied to antagonistic muscle, while patients are instructed to close their mouths and slowly breathe only through the nose in the case of vocal tics. In case of tics with premonitory urge, competing response is applied until the premonitory urge fades away. However in children, in which premonitory urge is rare, competing response may be helpful from the very beginning of each tic episode, considering the fact that tics come in bundle forms.

While HRT takes care of tic symptoms one by one, exposure and response prevention technique obliges a child patient to endure all tic symptoms at once. Although ERP is much less studied than HRT, there have been reports on its effectiveness, possibly even more so than HRT [35].

Other behavioral techniques such as relaxation training or contingency management can be used along with or adjunctively with the earlier mentioned techniques. The down side of these behavioral therapies is that it requires too much time, technique, and effort. The process takes about 12-14 sessions or several months. Behavioral therapies are more effective when patients develop close relationships with the therapist, and require much help from friends and families especially at a young age.

3) Pharmacological therapy

Physicians must take many circumstances into account when using drugs, rather than merely selecting which drugs to use. Since tic affects much more than just the patient himself, comorbid disorders and many other situations must also be considered in addition to the frequency and severity of the tic. Since the severity of the symptoms felt by the patient, parents, and teachers can be very different, different treatment plans must be used even in patients with the same severity. Moreover, it is important to remind them of the fact that pharmacological therapies are for mitigation of tic, not its complete termination.

Selecting which pharmacological therapy to use cannot be decided uniformly on all patients, since the patient's quality of life, side effects, and comorbid disorder must all be considered. For example, it would be fine to use a drug that causes slight weight gain on thin patients, but it would not be appropriate for obese patients. In addition, since the tic disorder repeatedly improves and deteriorates, it is difficult to determine whether the changes in symptoms are due to the applied drugs or just natural phenomena.

Dosage must also be tightly controlled by periodically re-assessing the symptoms. There is no set guideline on the duration of application of the drugs in case of improvement, typically it is maintained for 6-12 months after improvement, and under careful observation, it can be reduced gradually afterwards. In the process of gradual reduction, rebound phenomenon might appear, so it is helpful to explain this to the patients and families in advance.

Generally, observation and appropriate psychoeducation is enough for weak tic symptoms in the early stages. For persistent tics, however, treatment should be considered, depending on tic's interference with everyday life, physical problems and pain caused by the tic, and school problems (grades, bullying, etc.). If the mentioned problems are severe, pharmacological therapy alone or combined treatment along with behavioral therapy are recommended.

The efficacy of antipsychotic drugs, such as risperidone and aripiprazole, has been reported in several recent controlled studies, though the only FDA-approved medications for TS remain the two classical antipsychotics, haloperidol and pimozide [36,37]. Previous studies also reported the modest efficacy of the alpha agonists, clonidine and guanfacine. Alpha agonists are known as a good choice for patients with tics and ADHD, since both disorders may respond [31].

4) Treatment of comorbid symptoms

Most often seen psychiatric comorbid symptoms along with tic disorder are OCD and ADHD. These comorbid disorders often cause more severe problems than the tic itself, and treatment of these disorders often lead to improvement in tic. Therefore, it is typical to treat these first.

There are many reports that claim OCD-related pharmacological and behavioral therapies are less effective in OCD patients with tic disorder than patients without tic disorder. Similar to typical OCD primary treatments, CBT or serotonin reuptake inhibitor (SRI) are used for primary treatment of OCD patients with tic disorder. For those who are less responsive to SRI, reinforcement using low dosage anti-dopaminergic agents such as risperidone can be effective [38].

There have been many changes in treatment of ADHD in tic patients over the years. There have been case reports which claimed that central nervous system stimulants can worsen tic. This led to

the ban of application of such stimulants on tic and TS patients by the FDA. However, a randomized control study reported that this is not the case, and these drugs might actually mitigate the symptoms [39]. Therefore, a clear treatment guideline is currently absent. In ADHD patients with TS, α-2 adrenergic agonists or atomoxetine can be used. However, central nervous system stimulants are more effective in controlling ADHD symptoms.

7. Natural course and prognosis

Tic disorder usually appears at 3-8 years of age. Symptoms reach their peak at about 10-12 years and declines after puberty [11]. Tic symptoms are significantly reduced or disappear in 60-80% of patients in their late adolescence or adulthood [40]. Maturation of the central nervous system such as increased self-control capacity of the cerebrum and basal ganglia, and pruning process in late childhood and adolescence is the most convincing explanation for the decline of symptoms after puberty [41]. In addition, psychiatric comorbid disorders such as ADHD, OCD, or impulse control disorder are known to affect prognosis more than the severity of the tic symptoms themselves. Therefore, assessment and treatment of accompanied psychiatric problems are very important for positive prognosis.

DEVELOPMENTAL COORDINATION DISORDER

Individual with Developmental coordination disorder (DCD) are characterized by marked impairment in the acquisition and performance of motor skills. Motor impairments include delays in developmental milestones, clumsiness, poor balance, poor handwriting, poor sensorimotor coordination, poor postural control, and difficulty in motor learning [42]. DCD leads to many obstacles in a child's school or everyday life, such as dressing, feeding, and poor hand writing.

1. Epidemiology

According to DSM-5, prevalence of DCD in children aged 5-11 years is 5-6% (6-13% in some studies) [1], and the gender ratio is 2-7:1 with more males affected [43].

2. Pathogenesis

DCD is more common in infants exposed to alcohol during the prenatal period and steroids in postnatal period, premature infants, and low birth weight infants [44-46]. Cerebellar dysfunction might be responsible [47]. ADHD, learning disorder, and autism spectrum disorder frequently accompany DCD, and for this reason genetic commonality was discussed. The concordance rate with ADHD is between 35-50% [47]. However, twin concordance only applied to highly severe cases. No consensus has been established about the pathogenesis of DCD [42].

3. Differential diagnosis and comorbid disorders

Developmental coordination problems are associated with visual function impairment and certain neurological disorders (e.g. cerebral palsy, disability progression of the cerebellum, neuromuscular diseases) [47]. In intellectual disabilities, motor function skills correspond to the intellectual level of the patient. However, if motor problems are more severe than expected, and if it conforms to the diagnostic criteria of DCD, it can be diagnosed together with DCD. ADHD appears at about half of DCD patients [47]. Lack of motor skill can be attributed to either DCD or merely to inattention or impulsivity in ADHD patients, so careful observation is necessary. If the patient fits into both ADHD's and DCD's diagnostic criteria, both should be diagnosed. Autism spectrum disorder patients also require differential diagnosis since they might not be interested in sports that need complex motor skills. DCD patients often accompany autism spectrum disorder, and if the patient fits into both criteria, both disorders can be diagnosed at once [1]. Other comorbid disorders include language disorder, certain learning disabilities (especially, reading and writing), disruptive behavioral disorder, emotional disorder, and ophthalmic abnormalities [48-51].

4. Treatment

Regarding the fact that more than half of DCD patients carry the disorder to adulthood, appropriate intervention is needed. Until now, operation therapy, physical therapy, pharmacological therapy (e.g. CNS stimulants), and diet therapy (supplementation of fatty acid and vitamin E) have been cited as treatment techniques [52]. Existing treatment techniques can also be classified into process-oriented therapy, task-oriented therapy, and traditional physical/occupational therapy [52]. Process-oriented therapy focuses on bodily functions required to perform specific motor activities [52]. Examples include sensation integration therapy, kinesthetic training, and perception training. Task-oriented therapy focuses on the performance of specific motor activities itself and focuses on teaching patients specific motor techniques directly, and there-

by, stimulate participation in diverse social situation, such as home, school, etc. [52-55]. A recent meta-analysis has reported that task-oriented therapy, traditional therapy, and CNS stimulants are effective. Moreover, it reported process-oriented therapy as ineffective, and diet therapy as evidence-lacking [52].

5. Natural course and prognosis

Although improvement can be observed in the long run, DCD is maintained throughout puberty in 40% of patients [56]. Symptoms usually appear in early childhood; they start with delayed motor development and affect tasks that require motor coordination. If the disorder prevails until adulthood, the patient experiences difficulty in driving, acquiring new motor skills, writing, and using tools; this can severely affect work life. Difficult social life, lowered self-esteem, and behavioral problems are often seen in DCD patients, and if ADHD is accompanied, problems in academic achievement and social adjustment become much more severe; this makes long-term prognosis highly negative [57].

STEREOTYPIC MOVEMENT DISORDER

Stereotypic movement disorder is when a repetitive, hard to control, aimless motor activity interrupts everyday life or causes self-infliction of a child. Stereotypic movements are involuntary, rhythmical, and show certain patterns and intensity. It is also easy to guess in which body part the movement will be performed, and if attention is drawn to other body parts, it might become controllable. Examples include hand flapping, hand waving, body rocking, head banging, lip-smacking, chewing movements, self-biting, and hitting oneself [1].

1. Epidemiology

Repetitive movements are frequent and are observed in more than 60% of children 2-5 years of age [58]. Complex stereotypic movements are relatively rare, and in 10-20% of intellectual disability children, self-injurious behaviors are observed, with incidence increasing with the severity of intellectual disability [59].

2. Pathogenesis

Social isolation increases the likelihood of preoccupation in self-stimulation, which may lead to stereotypic movement disorder. Social stress or unrest can also worsen the disorder. Low intellectual level increases the risks of stereotypic movements, and decreases the responsiveness to intervention. Pathogenesis of the disorder is still unknown. Suggested hypotheses are [60,61]: a hypothesis that suggests the disorder is a kind of learned behavior and is maintained through continual reinforcement, a hypothesis that correlates the disorder with neurological development of the child, a hypothesis that sees the disorder as a kind of self-stimulation activity that can also be seen in isolated intellectually disabled children, and last but not least, a hypothesis that attributes the disorder to some kind of biochemical mechanism caused by genetic changes, getting the idea from the fact that the disorder is more often seen in autism or Rett syndrome patients [61].

3. Differential diagnosis and comorbid disorder

Stereotypic movement disorder can itself be the primary diagnosis, or can be secondarily diagnosed caused by other disorders [61]. Many neurogenetic syndromes accompany the disorder, and in all of such cases the disorders are all diagnosed.

Simple stereotypic movements are most frequent in infancy and early childhood, and can appear as normal responses. Body rocking can occur during waking up, and usually disappears with age [61]. Complex stereotypic movements are rare in a normally developed child, and can be suppressed by redirecting the attention or other stimuli.

Stereotypic movement can be one of autism spectrum disorder's symptoms, but lack of social communication and reciprocity seen in autism spectrum disorder are generally not present in stereotypic movement disorder. In case of autism spectrum disorder patients, stereotypic movement disorder is only diagnosed when self-injurious behavior is observed or when severe, treatment-requiring stereotypic movements are observed.

Distinction from tic is necessary; on average, the onset of stereotypic movement disorder is before 3 years of age, which is earlier than the onset of tic [62]. In tic disorder the body part at which the disorder appears keeps on changing, while in stereotypic movement disorder the pattern and form are consistent and fixed [61]. While tic disorder is more associated with eyes, face, head, and shoulders, stereotypic movement disorder usually appear more in arms, hands, and the whole body. While a tic episode prevails for less than one second, stereotypic movements are rhythmical and have a long duration. Both can decrease when attention is redirected.

Stereotypic movement disorder does not accompany repetitive behavior patterns related with obsessions, distinguishing it from compulsive behavior. Trichotillomania or skin picking disorder

can also be distinguished since they lack formalization, are not rhythmical, are body-centered repeated activity, and usually appear after puberty.

Diagnosis of the disorder must exclude habits, mannerism, paroxysmal dyskinesia, and positive genetic chorea. Neurological history and characteristics that are associated with symptoms of myoclonus, dystonia, tic, chorea, etc. should be assessed carefully.

4. Treatment

Behavioral and pharmacological therapies are used to treat stereotypic movement disorder. Severe cases, in which normal life is nearly impossible and self-injurious behaviors are observed, require pharmacological therapy. If other psychiatric problems such as tic disorder, autism spectrum disorder, ADHD, OCD, language and learning disorders exist, these must be treated beforehand.

Several techniques have been introduced in behavioral therapy. Examples include physical limitations to stereotypic movements, response prevention, non-contingent stimulation (stimulus-rich environment), and direct correction techniques such as contingency or positive reinforcement. Although physical limitation is effective, it might cause severe distress. Therefore, non-contingent stimulation is recommended [63].

Although there is no evidence that pharmacological therapy is more effective than behavioral therapy, if the case becomes severe and the patient cannot afford behavioral therapy, pharmacological therapy can be used. Anti-psychotic drugs such as risperidone, aripiprazole, or selective serotonin reuptake inhibitors (SSRIs) can be applied [61,64,65], and the effects might appear gradually and only result in partial improvement.

5. Natural course and prognosis

Stereotypic movement disorder usually appears before 3 years of age. Simple stereotypic movements are often seen in infancy, associated with acquirement of motor skills, and can be mitigated with time. Complex stereotypic movements can appear at or later than infancy. In the case of intellectual disability patients, the pattern and form of self-injurious activities may change over time, but stereotypic movements themselves can be maintained for several years [66].

CONCLUSIONS

Motor disorders often seen in childhood include tic disorder, developmental coordination disorder, and stereotypic movement disorder. The onset of these disorders is usually infancy or early childhood, and if appropriate intervention is not undertaken, these may prevail even after puberty and cause severe problems in everyday life. Many studies have been conducted, but causes or pathophysiological mechanisms of these disorders are not yet clear. Problems caused by the symptoms of the disorders may continually change depending on the developmental stage of the child, and there may be a significant gap in the actual discomfort of the child and what the others see. Therefore, comprehensive medical history taking, continuous observation of the changes in symptoms, and systematic assessment considering the child's developmental stage and current adaptive capacity are needed. Moreover, the child's family/school/social community must be taken into account as well as the evaluation of the child himself when diagnosing and treating the child.

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