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Chapter 2

Psychopathology in Down Syndrome

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Additional information is available at the end of the chapter

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Abstract

The main aim of this section is to provide clinicians with a guide to the prevalence of psychopathologies, associated factors, and their treatment in children with Down syndrome (DS). Attention-deficit/hyperactivity disorder (ADHD), behavioral disorders, depression, and autism are more common in DS than the normal population. However, the incidence of psychopathology is generally lower in DS than in other diseases that cause mental retardation. While writing this chapter, approximately 200 articles in electronic databases were scanned using the keywords "Down Syndrome and Psychopathology," "Down Syndrome and Mood Disorder," "Down Syndrome and Autism," "Down Syndrome and Anxiety," "Down Syndrome and Catatonia," and "Down Syndrome and Behavioral Disorder." Psychopathologies in DS will be presented in eight subtitles beginning with the most often diagnosed. It is important to perform psychological evaluations of patients with DS during routine follow-ups. Comorbid diseases (obstructive sleep apnea, cardiac pathologies, etc.) should be taken into account when choosing drugs.

Keywords: down syndrome, psychopathology, mental health

1. Introduction

Down syndrome (DS) is the most common chromosomal anomaly which is associated with intellectual disability (ID), typical physical features, and health problems. The incidence of DS is about 1–1.5 of every 1000 live births. DS is the most frequent genetic cause of mental retardation (MR) [1]. People with MR have behavioral, emotional, and psychiatric problems more often than the general population [2].

DS exhibits distinctive neurodevelopmental, neurocognitive, and psychopathological patterns when compared to other genetic syndromes leading to ID, albeit higher than the general population [3]. A 28.9% of the children with DS have psychiatric comorbidity [4]. The children with DS

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are more likely to have externalizing behaviors than their siblings and peers, including hyperactivity, impulsivity, inattention, tantrums, agitation, stubbornness, disruptiveness/argumentativeness, oppositionality, repetitive movements, sensory dysregulation, and speech problems despite being recognized as friendly, easygoing, good tempered, affectionate, and sympathetic individuals [3, 5, 6]. The rate of severe behavior disorder in children with DS is reported as 23% [7]. The 4- to 18-year-old children with DS are more likely to exhibit such externalizing behaviors compared to normal-developing controls; 6–8% of children with DS are diagnosed with attention-deficit/hyperactivity disorder (ADHD); and 10–15% of children or youth are diagnosed with behavioral or oppositional disorders [2]. Externalizing behaviors change into internalizing behaviors in adolescents with DS. Internalizing behavior problems such as withdrawal, shyness, low confidence, and depression are more common in adolescents and adults [2]. A longitudinal cohort study showed that the incidence of depressive disorders was 5.2% of the total sample of adolescents and adults (16 years) with DS [8]. Depressive symptoms can also be seen with increased maladaptive behaviors other than known symptoms deteriorating speech and adaptive skills and fluctuating motor symptoms. As in the general population, anxiety symptoms such as fear, trembling, flushing, and irritability can be observed in DS [9]. However, there is not enough data on the incidence and prevalence of anxiety symptoms in DS. Some have shown that the prevalence of obsessive-compulsive disorder (OCD) in DS ranges from 0.8 to 4.5% and not much higher than the general population. These rates may be low because it is difficult to assess the obsessions and compulsions in individuals with cognitive impairment. As for OCD, there is a lower prevalence of schizophrenia and bipolar disorder in individuals with DS [3]. In latest studies, the co-occurrence of DS and autism spectrum disorders (ASD) has increased ratio; approximately 6–10% of children have comorbid ASD [5]. Compared with the children with ASD in general, the children with DS are diagnosed with ASD in 6–16 years of age. The syndrome that may overlap with DS phenotypic social communication patterns may be difficult to define in the DS population due to behavioral diagnostic criteria [10].

The prevalence of DS was 5.9 per 10,000 general population. Point prevalence of mental disorder of any type varied from 23.7 to 10.8%; 2-year incidence varied from 14.9 to 3.7% [8]. This suggests that psychopathology is not seen in a minor proportion of individuals with DS. In this article, we aimed to define psychopathology in individuals with DS and to guide the clinicians in diagnosis and treatment.

2. Attention-deficit/hyperactivity disorder (ADHD)

ADHD is a developmental disorder with a prevalence of 5% in the community [11]. ADHD frequency in DS is 14–43.9% [12, 13].

It was thought that attention deficit and hyperactivity are caused by maturation retardation in the past years, and therefore there should not be an additional diagnosis other than mental retardation [14]. Diagnostic overshadowing has been used to describe this situation [15]. However, according to both the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) and the DSM-V, mental retardation is not an exclusion criterion for ADHD [16, 17].

ADHD has three main symptoms: inattention, impulsivity, and hyperactivity, which are disproportionate to mental age. These symptoms can be observed in children with DS, but impulsivity and hyperactivity are more prominent up to 36 months [18]. In a study in 14 DS children (aged 2–4 years), ADHD was diagnosed in 30% of the children [19].

The children with DS may have mental retardation in mild (IQ 50–70), moderate (IQ 35–50), or severe (IQ 20–35) levels [20]. Studies of whether there is a correlation between the symptoms of ADHD and the degree of mental retardation are contradictory [12, 19, 21, 22]. It is known that executive functions are inadequate in ADHD. DS is also known to be inadequate in executive functions (especially in process memory) [23, 24]. Visual and hearing loss, obstructive sleep apnea, and thyroid disease associated with DS may mimic symptoms of ADHD [12].

The most commonly used drugs in the treatment of ADHD are psychostimulants and atomoxetine. Psychostimulants are the first line of treatment [25–28]. However, cardiac pathology in 50% of DS patients lead to the preference of other drug groups such as alpha-adrenergic agonists in place of methylphenidate in the treatment of ADHD [29, 30]. In addition, the presence of decreased dopamine beta-hydroxylase and increased catechol-o-methyltransferase activity in DS also modifies methylphenidate efficacy [31]. In support of this view, the only study of ADHD treatment in DS was performed using guanfacine. Twenty-three children aged between 4 and 12 years were included in the study and given guanfacine treatment. The effect size of guanfacine for inattention was found to be 0.7, and the effect size for hyperactivity was found to be 0.9; no serious side effects were reported [18]. Thus, there is a need for more research for the treatment of ADHD in DS.

3. Conduct disorder

Conduct disorder as other psychopathologies is more common in children with mental retardation [32]. More than 10% of the children with DS were diagnosed with conduct disorder [33]. Conduct disorder prevalence in DS is lower than other pathologies causing mental retardation [34].

Externalizing behaviors in DS is more common than internalizing behavior [35]. In a study, which used the Child Behavior Checklist and included 211 children with DS, stubbornness (79%) and disobedience (74%) were reported. Stubbornness has been reported to be a characteristic of DS. In the same study, behavioral problems peaked between 10 and 13 years of age, and in accordance with clinical practice, externalizing behavior was reduced toward late adolescence and internalizing behavior was increased. However, in both adult and pediatric samples, it has been found that fighting (12%) and excessive physical aggression (6%) in individuals with DS are rare [36].

Some atypical antipsychotics approved by the Food and Drug Administration (FDA) for the treatment of aggression in autism are often used off-label in the treatment of aggression in patients with mental retardation [37]. Studies have shown that the use of atypical antipsychotics in DS peaked between 11 and 14 years of age. This age range is also the period when behavior problems are frequently seen in DS. Behavioral problems in DS are more common in

males than in females, and consistent with this, atypical antipsychotic use is more common in males [28, 36]. Thus, there is a need for new studies, especially on drug treatment.

4. Depression

The prevalence of psychopathology is higher in DS than healthy population [34]. However, psychopathology is less frequent in DS compared to other children with intellectual disability [3]. The prevalence of depression in DS is 11%; DS is also a risk factor for developing depression [38, 39]. Depression frequency is lower in children and adolescents with DS than adults [40].

Stress-related disorders, such as depression, are the result of complex interactions of external stressors and biological factors [41]. Cognitive impairment and inadequacy of problem-solving skills lead to social rejection and failure [42]. In DS, the total brain volume and hippocampus volume are smaller than the normal population, leading to an increased risk of depression [43, 44]. These structural changes in the brain are thought to be caused by a protein overexpression encoded on chromosome 21 [45]. It is thought that serotonin, an important neurotransmitter in brain development, is deficient in fetal life in individuals with DS and that this deficiency continues in adulthood and increases susceptibility to depression [46].

Diagnosing depression is difficult in children with DS due to various problems related to neurophysiological developments (retardation in nonverbal communication, delay in speech) [28]. The most common symptom of depression in DS is the loss of interest (95.4%). In addition, changes in sleep and appetite patterns (81.8%), agitation (72%), and anxiety (40.9%) are other common symptoms [47]. Suicidal thoughts and guilt are rare [48].

In a study, only half of the 56 patients with DS who were diagnosed with depression were found to meet the criteria for major depression according to the Diagnostic and Statistical Manual of Mental Disorders. This is thought to be due to the lack of separate diagnostic criteria for patients with mental retardation [49].

Depression in people with DS needs to be separated from hypothyroidism, because hypothyroidism is more common among people with DS than the normal population [50]. In addition, sleep apnea, which may mimic depression, may be diagnosed at a rate of 30–60% in DS [39, 51].

The most commonly used drug is selective serotonin reuptake inhibitors (SSRI), but there is no controlled study in this respect [52]. In a retrospective study involving 832 children and adolescents with DS, the rate of SSRI use was 9.6% for 5- to 11-year olds and 7.6% for 12- to 21-year olds [28]. In a study compiling case reports, antidepressant treatment response rate was found to be 50% [49]. In addition, electroconvulsive therapy and psychotherapies can be used in therapy [53–55].

5. Autism

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by restricted, repetitive behavior and interests and difficulties in social communication and

social interaction. The prevalence of autism in the world is about 1%, and approximately 45% of the cases are accompanied by intellectual disability. About 5–39% of ASD individuals have DS and 1–11% of DS individuals have ASD. Autism is more common among individuals with DS than the general population [56, 57].

ASD was reported in other chromosome abnormalities (21–50% of affected individuals have autism in fragile X syndrome, 24–60% in tuberous sclerosis complex, 50–81% in Angelman syndrome, 60–70% in Timothy syndrome, ~40% in Joubert syndrome, 5–20% in phenylketonuria, and 15–50% in CHARGE syndrome). DS is a chromosomal anomaly characterized by trisomy 21. Overlapping or co-occurrence of DS and ASD mechanisms is uncertain. Obstetric difficulties and/or fetal maldevelopment, congenital or early-acquired brain defects, vulnerability to anoxia, infection, or other harmful effects during the intrauterine or neonatal period as a result of chromosome abnormalities are some of the etiological factors suggested for DS and ASD in literature. Hereditary factors, epilepsy, and hypothyroidism are other medical conditions likely to cause autism in DS [13, 56, 58].

Meta-analyses and postmortem studies suggest that both autism and DS have neuropathological features in cerebellar and cerebral cortices such as heterotopic areas or focal abnormal gray matter density differences (amygdala, hippocampus, temporal lobe, cerebellum). These neuroanatomical differences, although not specific to autism and DS, may reflect changing functional organization patterns that are common to both [3, 56]. Cerebellum and brainstem white matters have increased volumes in individuals with autism along with DS in comparison to those without autism. These areas associated with stereotypes [59].

The children with DS are diagnosed with ASD in 6–16 years of age compared to the children with ASD only. The disorder, which may overlap with the phenotypic social communication patterns of DS, may be difficult to define in the DS population because the behavioral diagnostic criteria and regression occur later; an onset between 3 and 8 years of age may also be a reason for the delay in diagnosis [10, 57].

DS individuals without autism are communicated and socially motivated despite their verbal disabilities and show more advanced interpersonal relationships and play and leisure time skills than children with ASD. The evidence of autism are impairment of communicative gesture, mime, and facial expression; impairment in the ability to initiate or sustain conversation; social reciprocity; lack of eye contact; poor social orienting; infrequent social overtures; poor integration of verbal and nonverbal behaviors; lack of joint attention; restricted shared effect; inconsistent social responding (tendency to be alone, difficulty in interacting with children); constrained imitation; failure to develop functional means of communication; delayed speech (although motor milestones such as sitting and walking without support are within normal limits); habit of making irrelevant remarks; repeating the other person's phrases; echolalia; dull and repetitive play (such as rolling a toy over and over again); repetitive movements (such as frequent tapping of feet, flapping of arms, constant rocking of the body, compulsive touching of people, indiscriminate habit of feeling the texture of objects); undue attachment to certain objects; and distress over changes in environment [60, 61]. All these evidence are might also be seen DS individuals with autism. Individuals with DS alone may show language stereotypes, specific interests in parts of objects, rituals, specific body use, and strange behavioral patterns specific to DS. ASD in DS is diagnosed with specific autistic features that

include phenotypic behavioral features which may be determined by through and widely used screening tools (ADOS, CARS, M-CHAT) and DSM-V criteria [57].

The treatment and monitoring program should be structured according to the functional level and the disability areas of the affected person because each individual with DS has problems at different levels. Treatment approaches in ASD can be grouped into two categories as "educational treatments" and "pharmacological treatments."

There is no medical agent for treating the core symptoms of autism. But antipsychotic drugs (haloperidol, risperidone, aripiprazole) have been shown to effectively reduce challenging, stereotypic behaviors, irritability, tantrum, and hyperactivity. Educational approaches are the most effective approach to alleviate basic symptoms and increase functioning in autism [62, 63].

Early diagnosis of ASD in DS is important so that convenient educational, behavioral, rehabilitative, and therapeutic interventions and strategies are available to help ensure that children receive the best possible outcomes.

6. Obsessive-compulsive disorder (OCD)

Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions and compulsions. Obsessions are thought, impulse, and dreams in which attempts to disengage, if accepted as repetitive, disturbing, and illogical, have failed. Compulsions are repetitive behaviors and mental actions that appear to reduce obsessions and reduce anxiety caused by obsessions. OCD was classified with DSM-5 under the heading "Obsessive-Compulsive and Related Disorders" by subtracting it from the heading of "Anxiety Disorders" [64].

The prevalence of OCD in a follow-up study was reported as 3.5% [65], and other studies have shown that the prevalence of OCD among individuals with DS ranges from 0.8 to 4.5% and not much higher than the general population. These rates may be low because it is difficult to assess the obsessions and compulsions in individuals with cognitive impairment. OCD increases similar to depression and other internalizing behavior problems among adolescents and adults with DS.

The individuals with DS present with ordering and tidiness compulsions, which are the most commonly reported OCD symptoms. On the other hand "obsessional slowness" is described as a ritualistic behavior that is the part of compulsion in individuals with DS. In case reports, OCD symptoms such as compulsively turning off lights, insisting that all doors needed to be shut, aligning the objects like books and pictures, hoarding behaviors such as keeping objects (water bottles, sunglasses, and boxes), touching rituals (touching the floor in a ritualistic manner several times, touching each of clothes hangers routinely each morning), fastidiousness, spend excessive amounts of time in the bathroom, taking too long to complete daily routine (slowness in daily living skills, eating, and walking), perfectionism, and checking were reported.

The first line of pharmacological treatment for OCD includes SSRIs. Switching to another SSRI, augmentation with neuroleptics and the use of a serotonin norepinephrine agent are suggested as pharmacological treatment options for treatment-resistant OCD [66]. In literature,

it was shown that SSRIs were effective with OCD in DS, and neuroleptic augmentation was effective with treatment-resistant OCD in DS. Also, recent studies suggest that glutamatergic agents such as memantine are effective in treatment-resistant OCD in both individuals with or without DS [67].

7. Anxiety disorders

Fear and anxiety are necessary to survive by resisting danger and threat. Although it is an adaptive process, fear and anxiety may become pathological when they are incited by objects or situations that are not legitimately harmful or threatening and restrict the person's functioning [68]. Anxiety disorders include specific phobias, separation anxiety disorder, selective mutism, social anxiety disorder (social phobia), generalized anxiety disorder, panic disorder, panic attack specifier and agoraphobia, substance-/medication-induced anxiety disorder, anxiety disorder due to another medical condition, other specified anxiety disorders, and unspecified anxiety disorder [16].

DS exhibits distinctive neurodevelopmental, neurocognitive, and psychopathological patterns when compared to other genetic syndromes leading to ID, albeit higher than the general population [3]. People with ID often have more behavioral, emotional, and psychiatric problems than the general population [2]. Anxiety disorder is one of these psychiatric problems. Studies suggest that 10–22% of the individuals with ID have met diagnostic criteria for anxiety disorder; this rate is higher than the individuals with typical development (3–7%). Studies have found no difference in prevalence of anxiety among mentally disabled individuals between the genders [69]. As in the general population, anxiety symptoms such as fear, trembling, flushing, and irritability can be observed in DS [9]. However, there is no enough data on the incidence and prevalence of anxiety symptoms in DS.

Children with DS are more common to have externalizing behaviors than their siblings and peers despite being recognized as friendly, easygoing, good tempered, affectionate, and sympathetic individuals; these behaviors include hyperactivity, impulsivity, inattention, tantrums, agitation, stubbornness, disruptiveness/argumentativeness, oppositionality, repetitive movements, sensory dysregulation, and speech problems [3, 5, 6]. ADHD and anxiety comorbidities were found higher among individuals with DS-ID than in typically developed individuals [3, 69].

Treatment of anxiety disorders in childhood contains psychotherapeutic and psychopharmacological interventions, specifically cognitive behavioral therapy (CBT), behavioral therapy, and SSRIs. However, there is no enough study in literature for anxiety in DS and treatment of anxiety in DS [68]. There is a need for more studies on this subject.

8. Bipolar disorder

There is no study on the prevalence of bipolar disorder in children and adolescents, but the prevalence of bipolar disorder is 1% in life. Interestingly, it was found to be 0.3% in DS. This

rate is 1.6% in other disorders causing mental retardation. Bipolar disorder in DS is less common than the normal population, leading to the hypothesis that the susceptibility to bipolar disorder may be on chromosome 21. Recent studies have also shown that the susceptibility to bipolar disorder is in the 21q22 locus, which expresses the protein that regulates intracellular calcium concentration [70, 71]. Thus, individuals with DS with an extra chromosome 21 can compensate for the potential effects of the chromosome 21 with the disease [72].

9. Catatonia

Catatonia is a neuropsychiatric syndrome with typical motor indications and responds to electroconvulsive therapy and benzodiazepines [73]. The main signs are changes in motor activity, movement disorders (stereotype, grimas, and tics), changes in speech, impairment of oral intake, negativism, and urinary and gaita incontinence [74]. Neurological, autoimmune, and infectious causes must be excluded before the diagnosis of catatonia [75].

The prevalence of catatonia among children and adolescents with DS is not fully known, but case reports are available in the literature. In four case reports published in 2015, patients who were diagnosed with catatonia and did not respond to benzodiazepine treatment were treated with electroconvulsive therapy [48, 75].

The clinician should examine catatonia when regression—sudden loss of good acquired skills—is present. A significant number of adolescents with DS experience regression. In such a case, comprehensive psychiatric and physical examination is required for diagnosis. Physical examination is especially important for the exclusion of autoimmune and neurological diseases. A dramatic response to 1–2 mg lorazepam administration is a typical sign in catatonia. Symptoms such as mood swings, loss of interest and desire, and sleep and appetite disorders that can be seen in mood disorders can also be seen in the catatonia. The motor symptoms seen in the catatonia and the inability to respond to antidepressant and mood stabilizers in treatment are used in differential diagnosis. Individuals with DS generally do not respond to benzodiazepine therapy and require electroconvulsive therapy [27, 75, 76].

In conclusion, studies suggest that children with DS are at increased risk of having psychopathologies. The clinicians should not neglect the psychopathology in DS and must direct DS individuals to psychiatric examination and treatment. Nevertheless, there is a need for further studies about DS and psychopathology.

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