Down Syndrome Disintegrative Disorder: A Clinical Regression Syndrome of Increasing Importance

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Down syndrome disintegrative disorder (DSDD), a developmental regression in children with Down syndrome (DS), is a clinical entity that is characterized by a loss of previously acquired adaptive, cognitive, and social functioning in persons with DS usually in adolescence to early adulthood. Initially reported in 1946 as "catatonic psychosis," there has been an increasing interest among the DS community, primary care, and subspecialty providers in this clinical area over the past decade. This condition has a subacute onset and can include symptoms of mood lability, decreased participation in activities of daily living, new-onset insomnia, social withdrawal, autistic-like regression, mutism, and catatonia. The acute phase is followed by a chronic phase in which baseline functioning may not return. No strict criteria or definitive testing is currently available to diagnose DSDD, although a comprehensive psychosocial and medical evaluation is warranted for individuals presenting with such symptoms. The etiology of DSDD is unknown, but in several hypotheses for regression in this population, psychological stress, primary psychiatric disease, and autoimmunity are proposed as potential causes of DSDD. Both psychiatric therapy and immunotherapies have been described as DSDD treatments, with both revealing potential benefit in limited cohorts. In this article, we review the current data regarding clinical phenotypes, differential diagnosis, neurodiagnostic workup, and potential therapeutic options for this unique, most disturbing, and infrequently reported disorder.

Down syndrome (DS) is the most common cause of intellectual disability worldwide and occurs in ∼1 in 800 live births; it is most frequently caused by trisomy of chromosome 21 due to nondisjunction or translocation events.[1–3] In recent years, multiple centers have reported a specific pattern of developmental regression in individuals with DS, wherein patients lose language, behavioral, and cognitive skills that they previously acquired.[4,5] This condition has been more recently referred to as Down syndrome disintegrative disorder (DSDD). DSDD can be severe, with implications on both quality of life and the autonomy of persons with DS.[4] It is, therefore, key for all providers to be aware of DSDD to evaluate and potentially treat this condition. The etiology, pathophysiology, and therapeutic options for DSDD are currently unclear, although clinical data are rapidly emerging. Our focus for this review is to summarize the current knowledge of clinical features, potential etiologies, neurodiagnostic workup, and therapeutic options and to identify future areas of focus and research in this field.

abstract

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HISTORICAL REPORTS

In 1946, Rollin[6] described a cohort of 73 institutionalized adolescents and young adults with DS, 17 (23.3%) of whom were diagnosed with "catatonic psychosis." These individuals had an appropriate developmental period followed by behavioral changes, including agitation and harm directed toward self and others, during early adolescence (ages 11–14) that led their families to seek institutional care. Afterward, they experienced a deterioration phase marked by incontinence, mutism, apathy, social withdrawal, occasional behavioral outbursts, and psychosis, eventually leading to catatonia.

In 2000, Kerbeshian and Burd[7] provided a clinical description of autistic-like regression in a child with DS. In this study, the authors described an 8-year-old girl with DS who experienced autistic regression (loss of social and communication skills), loss of cognitive functions, and a rapid-onset insomnia, referring to this condition as autistic-like regression.[7] Subsequently, in 2015, Worley et al[4] presented similar case reports and characterized DSDD as a subacute onset of "autistic regression," cognitive decline resulting in a dementia-like state, occurring at an older age typical for autistic regression, and no other established diagnosis to explain the condition (Table 1).[8]

TABLE 1 Characteristics of DSDD

Criterion	Features
I	Autistic regression
II	Cognitive decline resulting in a dementia-like state
III	Older age at onset than at autistic regression
IV	No other diagnosis that may explain the condition

Adapted from Worley G, Crissman BG, Cadogan E, Milleson C, Adkins DW, Kishnani PS. Down syndrome disintegrative disorder: new-onset autistic regression, dementia, and insomnia in older children and adolescents with Down syndrome. *J Child Neurol.* 2015;30(9):1147–1152.

CLINICAL MANIFESTATIONS

The demographic profile of DSDD includes a postpubertal onset and an elevated female/male patient ratio of 2:1.[4,5] A defining feature of DSDD is regression of previously attained skills, notably in the domains of language, communication, and social skills. No formal criteria exist within the diagnosis of DSDD to define either regression or autistic-like behavioral regression; however, some groups have used the *Diagnostic and Statistical Manual of Mental Disorders* criteria of autism spectrum disorder to aid in standardization of phenotypic description for the latter phenomenon.[4,9] Diagnosis by using these guidelines involves new-onset impairments in social interaction; communication; stereotyped patterns of movement, behavior, and thought; and developmental delays.[9] At baseline, autism can be present in roughly 15% of children with DS; however, a previous diagnosis of autism was not observed in any of the studies reviewed in this report.[10] DSDD is an entity that is believed to be distinct and separate from autism spectrum disorder.

Beyond regression, symptoms of DSDD can be heterogenous and are reported with variability (Table 2). In 3 large studies, up to 87% of patients with DSDD were diagnosed with language regression, with symptoms ranging in severity from dysfluency to mutism.[5,11,12] Among patients in whom severity of language regression was quantified, 38% had partial language regression and 52% had mutism.[5,11,12] Mood symptoms are also reported and include depression (42%), social withdrawal (34%), and anxiety (16%).[5,12,13] In recent studies, catatonia was observed in 47% of cases labeled as DSDD, which is higher than rates originally reported by Rollin[6] (38%).[5,11,12] New-onset insomnia was also described in 43% of cases.[4,5,7,11,12] Pooled estimates from 4 studies revealed a 14% rate of psychotic symptoms, including delusions and hallucinations, in persons with DSDD.[4,5,11,12] Aggressive behavior was reported in 42% of patients.[2,5,11,13] As was highlighted by Mircher et al,[5] aggression in persons with DSDD may be directed toward self (auto-aggression) or others (hetero-aggression). A minority of patients with DSDD (12%) also had anorexia as part of their clinical presentation.[11,12]

Because there are no diagnostic criteria available, DSDD is best described as a clinical syndrome that should be considered in adolescents and young adults with DS and subacute-onset behavioral changes.[13] It is also key to appreciate

TABLE 2 Clinical Features Reported in DSDD

Clinical Feature	% (*n*/*N*)
Language regression[5,11,12]	87 (42/48)
Partial	38 (18/48)
Mutism	52 (25/48)
Catatonia[2,5,11,12]	47 (25/53)
Mood symptoms[2,5,12,13]	
Depression	42 (21/50)
Social withdrawal	34 (15/44)
Anxiety	16 (8/50)
Insomnia[4,5,11,12]	43 (25/58)
Aggression[2,5,11,13]	42 (17/40)
Delusions or hallucinations[4,5,11]	14 (8/56)
Anorexia[11,12]	12 (5/43)

that persons with DS may experience adaptive, social, or cognitive regression for reasons other than DSDD, making a complete workup critical in the assessment of these patients (see Evaluation and Differential Diagnosis). Compared with the typical onset of autistic regression in persons with DS, DSDD takes place when patients are older, typically between the first and third decade.[4,13] The acute regression appears to last for ~6 months and is followed by a chronic phase in which previous skills may not be completely recovered (Table 3). In 2 studies, it has been reported that 58% of persons with DSDD experience a partial or total recovery. Only 7.5% of patients experience additional worsening, whereas 35% of patients stabilize.[4,5] However, in patients with stabilizing DSDD, a complete recovery to the premorbid baseline condition appears to be infrequent.[2,4]

The imaging features of DSDD are heterogenous, and no defining characteristics have been identified. Across 5 studies, abnormal MRI findings were found in 26% of patients (n = 9 of 35).[4,5,11,12] The imaging findings were described to be dementia-like in 2 cohorts in which hippocampal atrophy was reported in 20% of patients (n = 4 of 20).[5,12] In other studies, there has been a failure to find any imaging findings associated with DSDD, which may reflect the significant heterogeneity of the study cohorts.[2,4,11]

THEORIES ON ETIOLOGY

Whereas the etiology of DSDD is not fully understood, 2 possible causes that have been proposed are immune dysregulation and psychological stress triggering neuropsychiatric presentations (analogous to Rollin's[6] original report). The demographic profile of DSDD includes a postpubertal onset and an elevated female/male patient ratio of 2:1 in the 2 largest studies to date.[4,5] This finding has raised the suspicion that inflammation may play a role in the etiology of DSDD because this demographic is mirrored in other inflammatory disorders such as multiple sclerosis and autoimmune encephalitis.[4,5,13,15] Additionally, recent research has revealed the presence of other autoantibodies, such as antinuclear antibodies, anti-microsomal antibodies, striational antibodies, thyroperoxidase antibodies, and anti-tissue transglutaminase antibodies, which have elevated levels in some individuals with DSDD.[11] These findings may be understood as a consequence of DS, which is generally associated with high serum levels of proinflammatory cytokines, high rates of complement protein consumption, and various other forms of immune dysregulation.[16] As

TABLE 3 Studies of Patients With Clinical Phenotypes Similar to DSDD

Authors, Year	Design	Patient Population	Summary of Results
Rollin,[6] 1946	Case series	17 cases of DS with catatonic psychotic living in an institution	Description of a period of behavioral agitation followed by decompensation characterized by incontinence, mutism, apathy, social withdrawal, occasional behavioral outbursts, and psychosis eventually leading to catatonia
Kerbeshian and Burd,[7] 2000	Case series	5 cases of DS and Tourette's syndrome, 1 case of childhood disintegrative disorder and DS	Description of new-onset insomnia, autism, and loss of cognitive skills in a patient with DS
Prasher,[8] 2002	Case series	357 patients with DS	DSDD regression is severe and gradual, lasting 2 y and followed by a chronic plateau; regression affected language, social, and cognitive domains
Castillo et al,[14] 2008	Case-control study	24 patients with DS and autism	50% (12 of 24) of patients with DS and autism lost previously acquired language, social skills, and communicative abilities; language loss occurred later in DS with autistic regression than in isolated autistic regression (62 vs 20 mo)
Akahoshi et al,[12] 2012	Case series	13 young adults with DS with acute neuropsychiatric symptoms	Patients with DS presented with depression, obsessive-compulsive behaviors, delusions, and hallucinations
Worley et al,[4] 2015	Case series	11 patients with DSDD	Late mean age of onset of DSDD (mean = 11.4 y); autism was new in onset in 8 of 11 patients and worsened in 3 of 11 patients; 91% (10 of 11) patients had cognitive decline; s82% (9 of 11) patients had new-onset insomnia
Ghaziuddin et al,[2] 2015	Case series	4 patients with DS and regression	Regression was accompanied by motor symptoms, including catatonia; recovery after a therapy with benzodiazepines and ECT
Jacobs et al,[13] 2016	Case report	Young adult male with DS	19-y-old patient presents with severe clinical deterioration; the patient presented with low mood, difficulty concentrating, anxiety, and motor symptoms
Mircher et al,[5] 2017	Case series	30 patients with DS and regression	Regression was seen at all levels of cognitive functions; regression was characterized by partial or total loss of activities of daily living; regression was associated with other psychiatric symptoms, which included catatonia, depression, delusions, and stereotypical behaviors; regression was preceded by severe emotional stress in all patients

the autoimmune etiology of several psychiatric syndromes becomes increasingly accepted, researchers speculate that some cases of DSDD may be driven by autoimmunity.[17,18]

Elevated serum and cerebral spinal fluid levels of anti-thyroperoxidase antibodies found in some patients with DSDD have led some researchers to propose Hashimoto encephalopathy (HE) as an underlying etiology. Across 4 studies, 35% of persons with DSDD (n = 16 of 46) had high titers of anti-thyroperoxidase antibodies, although the agreement between these studies is considered poor because rates range from as low as 20% (Mircher et al,[5] n = 15 tested) to as high as 82% (Worley et al,[4] n = 11 tested).[11,13] Epidemiological studies have revealed that thyroid disease has a greater prevalence in patients with DSDD than in the general population.[4] In addition, the rates of thyroid disease increase with time, as does the prevalence of thyroperoxidase antibodies, with rates up to 22% in asymptomatic patients.[19] The significance of anti-thyroperoxidase antibodies is unclear because steroid therapy, the gold standard treatment of HE, has revealed no clinical benefit in DSDD.[4] HE also differs from DSDD because it presents with seizures, headaches, hallucinations, and ataxia. Although HE can present as an isolated psychiatric illness, this presentation is rare in children.[20,21] Thus, additional studies are needed to fully elucidate the pathologic role of anti-thyroperoxidase antibodies in patients with both DS and DSDD (Table 4).

TABLE 4 Autoimmune Characteristics of DSDD

Authors, Year	Patient Population	Summary of Results
Worley et al,[4] 2015	11 patients with DSDD	Anti-thyroperoxidase antibody levels were elevated in 91% of patients with DSDD (10 of 11) vs 23% of patients with DS (5 of 21) ($P < .001$)
Jacobs et al,[13] 2016	Young adult male with DS	Negative results on autoimmune panel
Cardinale et al,[11] 2019	4 patients with DSDD	Anti-thyroperoxidase antibodies (n = 3 of 4), anti-TSH antibodies (n = 2 of 4), anti-microsomal antibodies (n = 2 of 4), anti-tTg antibodies (n = 1 of 4), antinuclear antigen antibodies (n = 1 of 4), anti-striational antibodies (n = 1 of 4)

anti-TSH, anti–thyroid-stimulating hormone antibodies; anti-tTg, anti-tissue transglutaminase.

An alternative hypothesis proposes that psychological stress may act as a trigger of regression in DSDD (Fig 1). In their studies, Stein et al[22] and Mircher et al[5] postulated that such behavioral changes may be a way for persons with DS to express distress in the context of their developmental delays. Across 3 studies, 86% of persons with DSDD (n = 30 of 35) reported identifiable life stressors preceding the onset of symptoms. In the largest study of 30 patients, Mircher et al[5] described a new school environment as the most common life stressor preceding a diagnosis of DSDD (51%).[11,22] Other common stressors were awareness of disability triggered by the wedding or departure of a sibling (23%), assault (17%), illness of a close one (13%), and overstimulation (10%).[5] Although notable, many children with DS experience similar stressful triggers and do not have similar neuropsychiatric changes, rendering stress-related triggers an incomplete explanation. Stein et al[22] also reported on the role of environmental changes as potential triggers for regression in DSDD. In their case study, the authors reported that a patient with DS developed reactive depression after moving to a new city and changing schools.[23] The authors postulated that the patient dealt with distress through complex behavioral and adaptive changes because she failed to express her distress with the usual verbal channels.[22] This description would exist on the spectrum of an acute stress reaction as opposed to a primary psychiatric disease and thus may explain the recovery noted in patients over time. Mircher et al[5] put forth a hypothesis that explains the susceptibility in terms of widespread dysregulation of serotoninergic and cholinergic circuits. If this were the case, DSDD may be amenable to treatment with selective serotonin reuptake inhibitors (SSRIs), which have only been explored in a few studies thus far.[24,25]

An exact etiology of DSDD remains difficult to identify, although components of immune dysregulation, psychiatric symptoms in persons with intellectual disability, and dysregulated cholinergic and serotonergic circuits may be involved (Fig 1). Although the role of inflammation in neuropsychiatric disease continues to evolve, the combination of neuroinflammation, autoantibody generation, and/or cytokine dysregulation could interface with existing psychological capacities to cope with external stressors and the baseline circuity of these responses. For this reason, additional investigation into the cause of this potentially polyfactorial phenomenon is needed.

EVALUATION AND DIFFERENTIAL DIAGNOSIS

At this time, DSDD is best described as a constellation of symptoms without a distinct etiology. Thus, clinicians should pursue a comprehensive psychosocial and medical evaluation of potential secondary causes of behavioral change and regression. In their article, Jacobs et al[13] provide a suggested diagnostic workup for such cases organized in 5 different tiers of testing (Table 5). The first 2 tiers are common causes of a new onset of psychiatric symptoms in young adults with DS, which include psychosocial stressors, depression, electrolyte disturbances, infections, liver disease, thyroid disorders, and

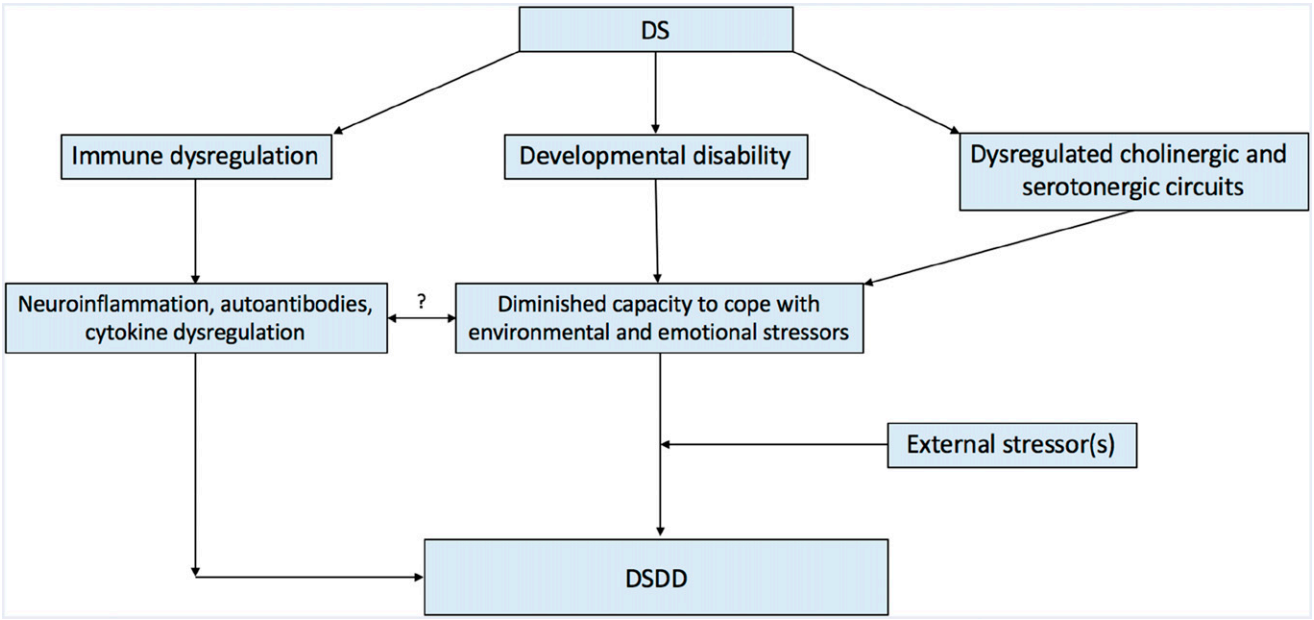

FIGURE 1
Diagram of proposed DSDD pathophysiology.

immunologic disorders. Common co-occurring conditions associated with DS should also be considered such as sleep apnea, acid reflux, celiac disease, and constipation. Another diagnosis in tier 2 is pediatric acute-onset neuropsychiatric syndrome, which displays some overlap with DSDD. Persons with pediatric acute-onset neuropsychiatric syndrome may present with a subacute onset of abnormal motor movements, tics, and obsessive-compulsive symptoms, although caution should be exercised before making this diagnosis, as well, given the heterogenous diagnostic and clinical criteria.

Multiple genetic conditions can occur in the same patient, and because DS is one of the most common genetic disorders, evaluation for other genetic disorders should be considered. Two important diagnoses to evaluate for are Fragile X syndrome and Rett syndrome, which are 2 important genetic causes of regression in early childhood. By the same token, inborn errors of metabolism are possible causes of regression and behavioral abnormalities in children and young adults. These syndromes are characterized by an inability to process certain metabolites, including amino acids, fatty acids, or organic acid. A final differential diagnosis to be aware of is Lesch-Nyhan syndrome, the presentation of which may closely resemble DSDD, except that onset is typically in infancy or early childhood. Patients with Lesch-Nyhan syndrome present with a combination of a regression of intellectual skills, dystonic movements, and compulsive self-mutilation because of a failure of purine metabolism.[26] These genetic conditions typically present in early childhood rather than adolescence and young adulthood like DSDD, but delayed diagnosis is plausible.

Finally, it is important to note that DS is associated with several psychiatric conditions. As previously mentioned, DSDD differs from other forms of autistic regression in the later age at onset, high female/male patient ratio, and presence of additional symptoms such as insomnia and catatonia.[4,5] In the presence of stressful triggers, primary psychiatric disorders, such as major depressive disorder, bipolar disorder, and anxiety disorders, may have symptoms that mimic a regression.[27] These disorders should be evaluated thoroughly because they unify the presence of environmental triggers and associated neuropsychiatric disease, although diagnosis can be challenging in persons with intellectual disability.[28] A key point to consider is that the presence of mild baseline psychiatric disease and exposure to stressful triggers may yield regression-like symptoms, although this likely exists along a complex spectrum. One final important differential diagnosis to consider is early-onset Alzheimer disease (AD), which continues to be an important differential for patients with DSDD.[11] Early-onset AD is common in patients with DS owing to the 3 copies of chromosome 21 (and thus 3 copies of amyloid precursor protein genes) carried by these patients. Early-onset AD differs from DSDD because of the later onset between the ages of 40 and 60 years and its steady and irreversible decline, as opposed to the subacute and partially reversible decline observed in DSDD.[29] However, AD onset may occur earlier than age

TABLE 5 Proposed Diagnostic Workup for Regression in Patients With DS

Tier	Diagnosis	Evaluation
Tier 1	Thyroid disorders: hypothyroidism, hyperthyroidism, HE	TSH, fT4, thyroperoxidase antibodies, thyroglobulin antibodies
	Electrolyte disturbance, infections, liver disease	Electrolytes, CBC, LFTs
	Vitamin deficiency	Folate, vitamin B_{12}, 25-OH vitamin D
	Celiac disease	Anti-tTg, total IgA
	Obstructive sleep apnea	Polysomnography
	Hearing loss	Hearing test
	Vision loss (cataracts, ulcers, etc)	Vision screen
	Constipation	Abdominal radiograph
	Depression	Depression screen
	Stress and anxiety	Screen for stressors
	Other psychiatric disorders	Psychiatric referral
	Other neurologic disorders	Brain MRI
Tier 2	Lyme disease	Serological testing
	PANDAS	Antistreptolysin O
	Seizure disorder	EEG
	Other immunologic disorders	Antinuclear antibodies, ESR, CRP
	Syphilis, HIV	RPR, HIV serology
Tier 3	Fragile X syndrome	Fragile X syndrome testing
	Rett syndrome	Methyl CpG binding protein 2
	Heavy metal toxicity	Serum levels of lead, manganese, mercury, zinc, nickel, thallium
	NMDA receptor encephalitis	Anti-NMDA receptor autoantibodies
	Microdeletion or microduplication syndrome	Chromosomal microarray
Tier 4	Aminoacidopathies	Plasma amino acids
	Organic acidurias	Urine organic acids, urine acylglycines
	Fatty acid oxidation disorders	Plasma acylcarnitines
	Mitochondrial disorders	Pyruvate, lactates
	Urea cycle disorders	Ammonia
	Ovarian teratoma (limbic encephalitis)	Ovarian ultrasound
Tier 5	Lesch-Nyhan syndrome	Hypoxanthine-guanine phosphoribosyl transferase gene mutation
	Porphyria	Aminolevulinic acid, porphobilinogen, hydroxymethylbilane synthase gene mutation
	Congenital disorders of glycosylation	Carbohydrate deficient transferrin
	Peroxisomal storage disorders	Very long chain fatty acids, phytanic acid, plasmalogens
	Lysosomal storage disorders	Urine glycosaminoglycans, urine oligosaccharides, urine sialic acid
	Other genetic disorders	Whole exome sequencing

anti-tTg, anti-tissue transglutaminase; CBC, complete blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; fT4, free thyroxine; IgA, immunoglobulin A; LFT, liver function test; NMDA, N-methyl D-aspartate; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; RPR, rapid plasma regain; TSH, thyroid-stimulating hormone; 25-OH, 25-hydroxycholecalciferol.

40 and may be exacerbated by factors similar to those reported in DSDD.[30]

Of note, the diagnosis of DSDD is based on clinical phenotype, and for this reason, it is important to realize that this syndrome may be produced by multiple causes. This is a necessary consideration regarding not only the need for a standardized workup but also the need for choosing the most appropriate intervention.

THERAPEUTIC INTERVENTIONS FOR DSDD

Several therapies have revealed some clinical benefit in patients with DSDD. Symptomatically, antipsychotics (eg, risperidone), SSRIs (eg, fluoxetine and sertraline), and anticholinergic drugs (eg, donepezil and rivastigmine) have been used to address many of the neuropsychiatric disturbances observed in DSDD.[4] In 3 recent studies, 25% of patients showed a response to SSRIs, which seem to improve mood symptoms, motor symptoms, and sleep disturbance.[12,31] Tamasaki et al[31] reported a case study of a 14-year-old boy with DSDD symptoms who was treated with donepezil, which led to a complete psychosocial recovery; however, the efficacy of cholinergic medications for cognitive impairment in individuals with DS is debatable, and they are not US Food and Drug Administration approved for children and adolescents.[32,33] Another therapeutic option for persons with DSDD is antipsychotic treatment. Across 4 studies, 70% of patients experienced at least some improvement in motor symptoms, sleep disturbance, and catatonia with antipsychotic therapy.[2,12,13]

Ghaziuddin et al[2] reported that high-dose benzodiazepines, such as lorazepam, could benefit patients with DSDD and catatonia. Across 4 studies, 91% of patients with DSDD and catatonia demonstrated at least a partial response to benzodiazepines; however, catatonia was unresponsive to benzodiazepines in only 1 patient.[2,11–13] Electroconvulsive therapy (ECT) has also been shown as an effective therapy for DSDD with catatonia that warrants careful consideration by clinicians.[2] However, ECT can have several complications, including the requirement of sedation, the potential for memory impairment and neurocognitive sequelae, and the need for repeated ECT sessions to maintain symptom remission; thus, it should be considered in conjunction with specialists experienced with its use in DS.[34] In a recent case report, administering high doses of the antipsychotic clozapine was the only effective treatment of catatonia and

TABLE 6 Previously Reported Experimental Therapies in DSDD

Authors, Year	Design	Patient Population	Summary of Results
Akahoshi et al,[12] 2012	Case series	13 young adults with DS with acute neuropsychiatric symptoms	A total of 10 of 11 patients responded to pharmacotherapy, and marked improvements were seen in 3 of 11; attempted pharmacotherapy included fluvoxamine, amantadine, haloperidol, and benzodiazepines
Ghaziuddin et al,[2] 2015	Case series	4 patients with DS and regression	High-dose lorazepam and ECT were associated with the improvement of catatonia; SSRIs, mood stabilizers, antipsychotics, and antiepileptic drugs resulted in no change or worsening of symptoms
Jacobs et al,[13] 2016	Case report	Young adult male with DS	Antipsychotics exacerbated the patient's catatonia; trazodone and high-dose benzodiazepines had no therapeutic benefit; the patient benefited from clozapine, which brought him back to 85% of his baseline status (as reported by the patient's mother)
Tamasaki et al,[31] 2016	Case report	Male teenager with DS	Initiated escitalopram after immune therapy with IV methylprednisolone and anticatatonia therapies; improvement over 4-wk period, although continued autistic features; initiated donepezil, with improvement in autistic features over an additional 4 wk
Cardinale et al,[11] 2019	Case series	4 patients with DSDD	Immunotherapy improved catatonia, insomnia, autism severity, cognitive decline, and psychosis in DSDD; regimens included IV and oral steroids, IV immunoglobulins, mycophenolate, and rituximab

IV, intravenous.

was started after other treatment options were exhausted.[13] It is crucial to consider that catatonia may be a symptom of DSDD because it may be easily mistaken for schizophrenia or another psychiatric disorder (Table 6).[2]

Newer therapies have been proposed that target the hypothesized autoimmunity etiology of DSDD. Cardinale et al[11] explored the use of various immunotherapeutic regimens in 4 patients with DSDD who had positive serum autoantibody screening results. Different regimens were attempted because of the side effects associated with many of these treatments, which required treatment discontinuation in many instances. The regimens included intravenous and/or oral steroids, mycophenolate mofetil, intravenous immunoglobulins, and rituximab. The clinical benefit in the domains of hallucinations, mood, autistic features, and insomnia was immediate in 3 of 4 patients, whereas 1 patient showed a clinical improvement in ∼3 months.[11] Catatonia was present in all patients who responded completely to immunotherapy. Approximately 50% of patients experienced an improvement in sleep disturbance and autistic behaviors. These results may lend more credence to the hypothesis of an immunologic component in the pathophysiology of DSDD for individuals with positive autoantibody screening results, but in this study, a limited cohort was analyzed, and additional studies with larger cohorts are needed.[4] However, as noted above, the presumed etiology may differ between cases; thus, the choice of therapeutic intervention should mirror this because multiple causes could produce the same clinical phenotype.

FUTURE DIRECTIONS

DSDD is a recently redefined constellation of symptoms, including mood lability, socio-communicative regression, loss of activities of daily living, psychomotor changes, and insomnia, which may permanently alter the adaptive and social functions of persons with DS.[4–6] Both patients and families are impacted by this condition. Additional research is urgently needed with particular focus on identification of the pathophysiology of the syndrome and the interplay between DSDD and other chronic comorbidities seen in patients with DS.

Prospective studies are needed to identify the effective therapies for each of the symptoms in DSDD. Several classes of therapies have revealed some clinical benefit (ie, benzodiazepines and ECT for catatonia and SSRIs for mood symptoms), but a standardized treatment guideline should be developed. Future studies will also be needed to elucidate the role of immune dysregulation in DSDD and the effectiveness of immunotherapies in larger cohorts.

Molecular biomarkers and radiologic hallmarks also need to be identified that correlate with the clinical findings. Additionally, truly separating the symptoms of DSDD from chronic comorbidities associated with DS will be a necessary component of future analysis. Finally, prospective studies are needed to understand the long-term prognosis and the effectiveness of therapies for this unique and troubling condition.

ABBREVIATIONS

AD: Alzheimer disease
DS: Down syndrome
DSDD: Down syndrome disintegrative disorder
ECT: electroconvulsive therapy
HE: Hashimoto encephalopathy
SSRI: selective serotonin reuptake inhibitor

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