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Down Syndrome Regression Disorder: Clinical Features, Diagnosis, and Therapeutics

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Introduction

Down Syndrome Regression Disorder (DSRD) is a neuropsychiatric condition affecting individuals with Down syndrome in the second or third decade of life. This condition was first reported in 1946 by Rollin¹ who described catatonic psychosis in a group of institutionalized persons with Down syndrome. For many years, this condition was presumed to be psychological or psychiatric in nature, with most symptomatic individuals receiving few or no diagnostic interventions.

By the first decade of the 21st century, in the setting of individuals with Down syndrome living longer and physicians' improved recognition of both autism spectrum disorder (ASD) and Alzheimer's disease (AD), DSRD remained a distinctive phenotype.²⁻⁹ Its characteristic symptom cluster— including sudden-onset neuropsychiatric disease, young-adult onset, fluctuating symptoms, and resistance to various treatment interventions— never truly fit with either ASD or AD criteria.

In the early 2020s a dramatic change in the evaluation of DSRD occurred, with more comprehensive phenotyping, neurodiagnostic testing, and treatment data coming to light. Multi-center data collected on patients with DSRD created a new paradigm for understanding this phenomenon.¹⁰⁻¹²

Clinical Signs and Symptoms

In 2021, an international group of physicians with expertise in Down syndrome was convened to develop clinical and diagnostic criteria for DSRD ([Table 1](#)).¹³ Individuals with DSRD may exhibit any combination of symptoms but they must have a non-tic movement disorder to meet criteria. This is often in the form of catatonia, which is prevalent in up to 75% of individuals with DSRD.

In its currently intended usage, DSRD describes a symptom-complex rather than a specific etiology. The diagnosis of DSRD is called “possible” when three or more symptom clusters are present or “probable” when six or more symptom clusters are present. This format allows for a lower threshold to initiate diagnostic investigations, given the potential therapeutic impact. These criteria are set for revision in 2027 per the original study team.

Diagnostic Testing Recommendations

There are no known biomarkers for DSRD so no laboratory tests can confirm this condition. As such, DSRD remains a diagnosis of exclusion. The study team convened in 2021 has published recommended diagnostic tests to rule out known conditions which can mimic DSRD ([Table 2](#)).¹³ These tests are broken down into two categories: those recommended for all patients meeting criteria for DSRD and addi-

tional testing as clinically indicated. Of note, many of the clinically-indicated tests are also ones that align with the American Academy of Pediatrics' guidelines for the care of adolescents and the [GLOBAL Medical Care Guidelines for Adults with Down Syndrome](#).¹⁴⁻¹⁶ Historically, the yield of serum-based diagnostic testing has been low in individuals with DSRD¹¹ although important mimics of this condition can be ruled out including hypothyroidism, metabolic derangement, anemia, and vitamin deficiencies. Additionally, cell-based autoimmune encephalitis panels (such as those provided through the Mayo Clinic) can be critical in ruling out more well-established forms of autoimmune encephalitis such as those associated with anti-NMDAR autoantibodies.

In individuals with Down syndrome who have suspected DSRD, an EEG is an important diagnostic test to rule out epilepsy and more rare epileptic conditions, such as Landau-Kleffner syndrome. This is particularly important given that the rates of epilepsy are elevated in children and young adults with Down syndrome.^{17,18} EEG interpretation can be challenging, however, as there are high rates of EEG abnormalities in this population at baseline and the patient may not have had an EEG at a pre-regression time point. That said, EEG can be used as an objective biomarker of improvement should abnormal EEG patterns resolve.

Magnetic resonance imaging (MRI) using a high-powered 3-Tesla magnet with and without

contrast can help rule out structural, inflammatory, and cerebrovascular mimics of DSRD. Additional diagnostic testing can be performed when appropriate, although the overall yields on positron emission tomography (PET), single-photon emission computed tomography (SPECT) and magnetic resonance spectroscopy (MRS) have been very low. Spinal imaging and magnetic resonance angiography are often not helpful for diagnosing DSRD unless there are other clinical symptoms such as lower extremity weakness or transient focal neurological deficits, respectively. Although neuroimaging in DSRD has not revealed a sensitive or specific biomarker to confirm the diagnosis, susceptibility-weighted imaging (SWI) abnormalities in the basal ganglia ([Figure 1](#)) may provide a diagnostic and therapeutic benefit.¹⁹ Multiple studies have shown that this type of signal abnormality is associated with up to an 8 times higher likelihood of response to immunotherapy, particularly IVIg.^{11,19-20} These neuroimaging findings are thought to be linked with dysregulated interferon responses as they are also observed in other interferonopathies such as Aicardi-Goutières syndrome.¹⁹

To diagnose active neuroinflammation, the gold standard is lumbar puncture. Although difficult to obtain, this test has become one of the most important for individuals with suspected DSRD. While only observed in 17-20% of cases, the presence of pleocytosis, high total protein, elevated IgG index, and oligoclonal banding indicate an active neuroinflammatory process

and warrant immediate consideration of immunotherapy.^{11,19,21} The capture rate for this test appears to be time-dependent with dramatically lower yield of abnormalities 12 months after the onset of symptoms,²⁰ emphasizing the importance of early obtainment. Finally, testing of cerebrospinal fluid (CSF) with a cell-based autoimmune encephalopathy panel is critical for ruling out antibody-mediated autoimmune encephalitis, as the yield of CSF studies is superior to serum alone.²²⁻²⁴

Mimics

As DSRD is a disease of exclusion, multiple layers of testing are required to arrive at this diagnosis.¹³ While burdensome, these tests are necessary to rule out rare neurological and systemic disorders with phenotypic overlap.²⁵

In a cohort of 266 individuals evaluated for DSRD, the most frequently-diagnosed neurologic conditions were autism spectrum disorder (76%), epilepsy (9%), and cerebrovascular disease (6%).²⁵ Additional diagnoses included untreated/diagnosed celiac disease, hypothyroidism, autoimmune encephalitis and traumatic brain injury. Of note, clinical features that were predictive of non-DSRD diagnoses included focal neurological deficits, early age at onset (defined as <8 years), discrete spells, isolated language deficits, and the absence of bradykinesia and catatonia.²⁵

Although autoimmune encephalitis has pheno-

typic overlap with DSRD, multiple studies have failed to identify a specific antibody in either serum or CSF that could cause this condition. As such, DSRD is currently conceptualized as an inflammatory encephalopathy unique to individuals with Down syndrome, as opposed to a form of autoimmune encephalitis.

Given the frequency of diagnostic mimics presenting for referral, particularly in the setting of greater knowledge of DSRD in the community, use of established diagnostic criteria and comprehensive testing is critical to arrive at the correct diagnosis. Psychiatric disorders, given their symptomatic overlap with DSRD, must be clinically ruled out by a multi-disciplinary team.²⁶ For more information on common psychiatric concerns in individuals with Down syndrome, see the article, [*Mental Health: Diagnosis and Treatment of Adults with Down Syndrome*](#).

Therapeutics

There is no established treatment for DSRD nor any completed randomized controlled trials (RCTs), making multi-disciplinary assessment critically important.²⁷ Therapeutic interventions may be tailored to a combination of both clinical symptoms (e.g., catatonia) and the results of neurodiagnostic tests (e.g., EEG, MRI, or lumbar puncture).²⁸ Regarding the former, consultation with a psychiatrist who has experience prescribing psychiatric medications to individuals with developmental disabilities is highly recommended. Regarding the latter, several

multi-center studies have demonstrated that specific neurodiagnostic abnormalities warrant early immunotherapy use.^{11,12,19,21}

Monitoring for clinical response is complex and requires a combination of clinical and objective assessment. Objective assessments include the Bush-Francis Catatonia Rating Scale (BFCRS), the neuropsychiatric inventory questionnaire (NPI-Q), the Clinical Global Improvement Scale (CGI), and a timed 25-foot walk (25FW). Measures of adaptive skills like the Vineland-3 Parent/Caregiver form or the Adaptive Behavior Assessment System-3 can gather information about adaptive functioning either before regression or during treatment.

Benzodiazepines

Benzodiazepines, such as lorazepam, are considered the gold standard for management of catatonia in any individual and have been previously demonstrated to be safe and effective for individuals with DSRD.^{11-12,29-31} Anecdotally, doses up to 2 mg three times daily are common. Monitoring clinical improvement using objective measures such as the BFCRS can be beneficial. In two recent multi-center studies, response rates to lorazepam were as high as 70%.^{11,12}

Psychotropic Medications

Selective serotonin reuptake inhibitors (SSRIs) are commonly used in the treatment of psychiatric disorders in individuals with Down syndrome. In DSRD, SSRIs often serve as adjunct treatments for catatonia (in addition to

benzodiazepines) as opposed to direct treatments for depression. These medications are effective and well tolerated.^{11-12,32-33} Anecdotally, fluoxetine is the most commonly used SSRI, although fluvoxamine can be considered in cases where obsessive-compulsive behaviors are co-morbid or impacting a person's function.

Antipsychotics

Use of antipsychotics in the management of DSRD should be limited to individuals with refractory insomnia, agitation, hallucinations or delusions, or who may pose a threat to self or others. Although effective at controlling symptoms,^{11-12,32,34} these therapies are not disease-modifying and may cause significant side effects. Anecdotally, atypical antipsychotics such as quetiapine, lurasidone, risperidone, and aripiprazole have been used and titrated to effect. Having a psychiatrist on the care team may be beneficial in cases of antipsychotic use, as these therapies can cause bradykinesia and other movement disorders. These side effects can make the existing catatonia worse, complicating interpretation. As such, it is prudent to consider alternatives to antipsychotics when appropriate, particularly when treating insomnia. For insomnia, consider non-SSRI antidepressants (trazodone), orexin antagonists (suvorexant), alpha-2 agonists (clonidine/guanfacine) and non-benzodiazepine hypnotics (zolpidem, eszopiclone, etc.).

Immunotherapy

As previously noted, individuals with DSRD and specific neurodiagnostic abnormalities can be highly responsive to immunotherapy.^{11-12,21,35-36} Intravenous immunoglobulin (IVIg) is considered the gold standard immunotherapy for DSRD at this time and is administered with a starting dose of 2 g/kg, typically over two days, with a maintenance dose of 1g/kg monthly thereafter. Individuals with DSRD often do not respond to IVIg right away, with a median time of three months to clinical improvement. In individuals who respond to IVIg, therapy should be limited to one year after a clinical plateau is reached, after which the patient can be weaned off treatment.²¹ In this study, approximately 50% of patients were able to wean off IVIg following one year of clinical stability. In patients failing this regimen, re-starting IVIg improved symptoms once more, although the exact duration of use after reinitiation remains unknown. While IVIg appears to be well-tolerated when infused either at medical centers or at home, one must remain vigilant for side effects such as anaphylaxis, aseptic meningitis, clotting/thrombosis, and liver enzyme elevations.^{37,38}

The use of second-line immunotherapy is limited currently. Although there are several studies investigating the efficacy and safety of therapeutics such as mycophenolate, mofetil, rituximab, tofacitinib, and azathioprine, more data are needed.¹¹

Electroconvulsive Therapy (ECT)

The management of medically refractory catatonia may require the use of ECT. This therapy has shown high efficacy in individuals with DSRD,^{11,30-31} particularly those without neurodiagnostic abnormalities. Anecdotally, individuals with DSRD who require ECT often have difficulty weaning off this therapy, necessitating long durations of treatment with uncertain side effects. In response to concerns of long-term and repeated sedation, some healthcare professionals have explored transcranial magnetic stimulation (TMS).^{39,40}

Clinical Trials and Future Research

At present, there is one clinical trial actively enrolling individuals with DSRD, who will be randomized to 12 weeks of lorazepam, IVIg, or tofacitinib. Other open studies are attempting to identify clinically meaningful biomarkers for DSRD and the mechanisms by which DSRD occurs, so reaching out to centers with specialized programs in this area may be beneficial. For inquiries on research opportunities we suggest reaching out to the National Down Syndrome Society (health@ndss.org), the Linda Crnic Institute (dsresearch@cuanchutz.edu), or Children's Hospital Los Angeles (dsresearch@chla.usc.edu).

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Table 1: Clinical criteria for the diagnosis of DSRD.

Category	Criteria	Possible DSRD	Probable DSRD
Symptom onset	Onset of new neurologic, psychiatric, or mixed symptoms over a period of <12 weeks in previously healthy individual with Down syndrome	Yes	Yes
Clinical evidence of neurologic dysfunction	<ol style="list-style-type: none"> 1. Altered mental status or behavioral dysregulation <ul style="list-style-type: none"> - Anorexia/decreased oral intake or hyperphagia - Confusion/disorientation - inappropriate laughter - Encephalopathy 2. Cognitive decline <ul style="list-style-type: none"> - Apathy - Abulia and/or avolition - Acute memory impairment (including new difficulty with recall) 3. Developmental regression with or without new autistic features <ul style="list-style-type: none"> - Social withdrawal - Loss of previously developmental acquired milestones - Inability to perform activities of daily living - Stereotypy - Rigidity around routine changes - Decreased eye contact 4. New focal neurologic deficits on examination and/or seizure 5. Insomnia or circadian rhythm disruption 6. Language deficits <ul style="list-style-type: none"> - Expressive and/or receptive aphasia - Global aphasia (mutism) - Whispered speech 7. Movement disorder (excluding tics)* <ul style="list-style-type: none"> - Catatonia - Bradykinesia - Freezing - Gait disturbance 8. Psychiatric symptoms <ul style="list-style-type: none"> - Anxiety - Delusions or hallucinations - Obsessive compulsive tendencies - Aggression/agitation 	>3 symptom clusters present	>6 symptom clusters present
Exclusion of other etiologies	Reasonable exclusion of alternative causes of regression including other systemic and central nervous system disorders. Other primary psychiatric disorders are also considered exclusionary.	Yes	Yes

* Must be included as one of the symptom clusters for possible or probable diagnosis.

Table 2: Diagnostic testing for individuals with suspected DSRD.

	All patients	As clinically indicated
Diagnostic Imaging	Brain MRI with and without gadolinium contrast on a 3T scanner	MRI spine with and without contrast PET/SPECT imaging MR angiography of the head and neck MR spectroscopy
Blood tests	Ammonia CBC w/differential CMP ESR CRP Lipid panel HbA1c B12 level Vitamin D 25-OH level TSH w/reflex T4 TPO antibodies Anti-thyroglobulin stimulating hormone receptor ANA Celiac serology or panel Cell-based autoimmune encephalitis panel	Infections testing ^{a,b} dsDNA Complement 3 and 4 Immunoglobulin levels Cytokine panel Celiac panel ASO Anti-DNAse B Vitamin B1 level Methylmalonic acid Vitamin B6 level Iron level, TIBC, and Iron Saturation Selenium level Heavy metal screen (lead, manganese, mercury, zinc, nickel, thallium) Myelin oligodendrocyte glycoprotein (MOG) antibodies (if not covered in cell-based panel) Lactate Advanced biochemical profiling (neurometabolic disorder evaluation) Fragile X testing Chromosomal Microarray Whole exome sequencing
Urine tests	n/a	Urinalysis with reflex culture Urine toxicology Total porphyrin and porphobilinogen Organic acids Acylglycines Glycosaminoglycans Oligosaccharides Sialic acid

Lumbar puncture	Cell count with differential	Infectious testing ^{a,b}
	Total protein	Opening Pressure
	Glucose	Neopterin
	Gram stain and culture	Angiotensin converting enzyme (ACE)
	IgG index	Lactate
	Oligoclonal bands	Pyruvate
	Cell-based autoimmune encephalitis panel	CSF amino acids
		Alpha aminoapodic semialdehyde
		Folate receptor antibody assay
		5-Methyltetrahydrofolate
	Tetrahydrobiopterin	
	Neurotransmitter metabolites (homovanillic acid, 3-0-methyl-dopa, and 5-hydroxyindole acetic acid)	
	Pyridoxal 5'-phosphate	
	Sialic acid	
	Succinyladenosine	
	Sepiapterin and dihydrobiopterin	
	Amyloid-beta 42/40	
	Phosphorylated tau	
Electroencephalogram	Routine (60 min) EEG	Prolonged EEG (4-6 h) Overnight EEG (24+ h)
Other testing	n/a	Polysomnogram (OSA evaluation) Audiogram (hearing evaluation) Neurocognition assessment

^a Potential bacterial/protozoal infectious testing: *Borrelia burgdorferi*, HIV, *Listeria monocytogenes*, *Mycoplasma pneumoniae*, *Mycobacterium tuberculosis*, *Treponema pallidum*.

^b Potential viral infectious testing: adenovirus, enterovirus, Epstein-Barr virus, herpes simplex virus 1 and 2, human herpes virus 6 and 7, influenza virus A and B, John Cunningham virus, measles, rabies, varicella zoster, west Nile virus and other region-dependent viral testing.

Figure 1: Two examples (A and B) of axial susceptibility-weighted images of bilateral basal ganglia abnormalities observed in individuals with Down Syndrome Regression Disorder. White arrows point to the areas of SWI signal abnormality. ¹⁹

