Immunotherapy in selected patients with Down syndrome disintegrative disorder

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PUBLICATION DATA
Accepted for publication 25th October 2018.
Published online

ABBREVIATIONS
DSDD Down syndrome disintegrative disorder
ECT Electroconvulsive therapy
IVIG Intravenous immunoglobulin

Down syndrome disintegrative disorder (DSDD) is an increasingly identified condition characterized by cognitive decline, autistic characteristics, insomnia, catatonia, and psychosis in adolescents and young adults with Down syndrome. Previously we reported a higher rate of autoimmune thyroid disease in these patients compared with unaffected individuals with Down syndrome. We therefore hypothesized DSDD may in some cases be immune-mediated. Here we report four cases of DSDD treated with immunotherapy. Families were interviewed retrospectively for symptoms of cognitive decline, autism, catatonia, psychosis, and insomnia before and after treatment, using established scales where possible. Medical records were reviewed for evaluations and treatment. All four patients received intravenous immunoglobulin with or without additional immunotherapy. Significant improvements were seen in catatonia, insomnia, autistic features, cognition, and psychosis. In this small case series of patients with autoimmunity, core symptoms of DSDD improved significantly after immunotherapy. This supports the hypothesis that, in some patients, DSDD is immune-mediated. Immunotherapy should be considered in the treatment of DSDD, particularly in patients with a history of autoimmunity.

A small subset of older children and young adults with Down syndrome has been reported to experience a characteristic acute to subacute cognitive decline with autistic features and insomnia.1 This decline, which Worley et al.1 have descriptively termed Down syndrome disintegrative disorder (DSDD), may also feature symptoms of catatonia, as reported by Ghaziuddin et al.2 DSDD is becoming increasingly recognized by Down syndrome specialists worldwide, yet the clinical phenotype has not been well defined and its etiology remains unclear.

Patients with DSDD were seropositive for thyroperoxidase antibodies at a rate significantly higher than in a control group of age-matched individuals with Down syndrome.1 Although their symptoms differed from those of Hashimoto encephalopathy,3 these findings raised the possibility that DSDD may be immune-mediated. Down syndrome is associated with increased rates of autoimmune disease and a recent proteomics study found that people with Down syndrome have elevated levels of several proinflammatory cytokines and increased complement consumption.4

In our experience, medications aimed toward symptomatic management of patients with DSDD, including neuroleptics, selective serotonin reuptake inhibitors, donepezil, memantine, and benzodiazepines, are largely ineffective. Correction of hypothyroidism similarly does not affect the course of the disease. The natural history of DSDD is spontaneous improvement over the course of several years but rarely with complete resolution of the encephalopathy.1 Given the possible immune etiology, we hypothesized that patients with evidence of autoimmunity would recover more completely and expeditiously with immunotherapy.

This retrospective, descriptive case series presents the response to immunotherapy in a small cohort of patients with DSDD who had evidence of autoimmunity.

This study was approved by the Duke University Medical Center Institutional Review Board. Consent for participation was obtained from parents who had legal guardianship, or from patient and parent otherwise; assent was obtained when possible. Patients with Down syndrome and a history of acute or subacute cognitive decline were identified by physicians in the Duke Down syndrome clinic between 2014 and 2016. Inclusion criteria were onset of symptoms after age 10 years, treatment with immunotherapy, and follow-up for at least 1 year after initiation of therapy. This resulted in identification of five patients.

One patient was excluded from the case series because she did not present until 4 years after symptom onset and received an incomplete course of immunotherapy,
consisting of only one corticosteroid treatment. She had no clinical response to the corticosteroids but has had mild spontaneous improvement over the 2 years since, with persistent abnormalities.

Data were gathered both by retrospective chart review and a structured parent interview including patient demographics, disease characteristics, treatment course, and long-term outcomes.

Standard questionnaires were used to interview parents in person or by phone. Symptoms before decline, at time of treatment, and at the end point were elicited. Domains covered included cognition, autism, catatonia, insomnia, psychosis, and neurologic conditions. Scales used to guide interviews were DSM-5 criteria for autism spectrum disorder, the Bush-Francis Catatonia Rating Scale, and the Athens Insomnia Scale. Because the study was performed retrospectively, the Bush-Francis Catatonia Rating Scale did not include physical exam findings. In addition to parent interviews, a chart review was conducted for each case, including the clinical history, work-up (Table I), and treatment course (Table II).

**CASE SERIES**

**Patient 1**
Patient 1 was a social 17-year-old female with mild intellectual disability. She was able to perform all activities of daily living and did well in school. She was diagnosed with Graves disease at age 7 years with positive-titer thyroperoxidase antibodies and was treated with radioisotope thyroid ablation followed by chronic hormone replacement. She had subsequent antibody seronegativity. At age 17 years, 2 weeks after an influenza immunization, she developed acute onset insomnia followed by autistic characteristics, catatonic symptoms, cognitive decline, and hallucinations. Her IQ decreased from 70 to 32. She became unable to read and perform activities of daily living and was incontinent of urine and stool. She was hospitalized for 3 months and treated for psychosis with haloperidol, fluoxetine, and lurasidone. Her condition stabilized, and these medications were gradually discontinued. She slowly recovered over the next several months. The episode lasted 8 months in total.

At age 19 years she had a second episode consisting of sudden-onset, severe insomnia, cognitive and language decline, and catatonia (Table I), again preceded by an influenza immunization. There were no apparent psychological stressors. She was admitted to the hospital where she had a seizure. She had normal magnetic resonance imaging (MRI) and cerebrospinal fluid studies (Table I). Her catatonia did not respond to lorazepam. She was treated with high dose methylprednisolone 1 week after the onset of symptoms, resulting in prompt and dramatic improvement. Within 1 month she developed steroid-induced myopathy, so she was transitioned to monthly intravenous immunoglobulin (IVIG). Mycophenolate was started and then discontinued because of cytopenia. She had a robust response to IVIG, fully regaining and even surpassing previous capabilities, with complete resolution of her catatonia, autism, insomnia, and seizures. Initial attempts to gradually discontinue IVIG resulted in relapse. After 18 months, the IVIG was discontinued successfully and she has no residual symptoms (Table SI, online supporting information).

**Patient 2**
Patient 2 was a 23-year-old female when she presented to our hospital. Several months prior, she had been diagnosed with Graves disease and had been physically assaulted at school. She later experienced acute onset of severe psychosis with auditory hallucinations and erratic outbursts, followed by insomnia, catatonia, and autistic features. She had a normal brain MRI and laboratory findings except anti-thyroperoxidase and thyrotropin receptor antibodies and mildly elevated cerebrospinal fluid protein.

She received high dose methylprednisolone for 5 days followed by an oral steroid taper, with immediate improvements in cognition, catatonia, and mood. She continued to have language deficits, so IVIG was added. Over the next few months her social behaviors, catatonia, and cognition continued to improve, but abnormalities persisted. Rituximab was added with some improvement in core symptoms, but she developed emotional lability, agitation, and repetitive behaviors which did not respond to benzodiazepines. Electroconvulsive therapy (ECT) was then initiated and her aggressive outbursts and repetitive behaviors resolved. She continues on rituximab and IVIG every 6 months and no longer receives ECT. She has returned to near-baseline, her only residual symptom being mild insomnia.

**Patient 3**
Patient 3 was a 25-year-old female with moderate intellectual disability working as a teacher’s assistant. Three months before symptom onset there was a flood in her home. Immediately before onset there was a change in her job responsibilities. She then experienced a subacute decline, beginning with disorganization and anxiety. Over the course of several months, she had cognitive and language decline, speaking only in short phrases and becoming unable to follow even one-step commands. She also developed impulsivity, emotional lability, aggression, stereotypies, and auditory hallucinations.

Her evaluation at that point revealed positive titer antithyroperoxidase and thyroperoxidase antibodies. She was treated with high dose methylprednisolone followed by an oral prednisone taper. She then received IVIG every 3 months for 1 year. Within a few months, her catatonia, autistic features, and insomnia resolved, but she still has behavioral outbursts and auditory hallucinations that have not responded to neuroleptic treatment.

**What this paper adds**
- Immunotherapy may improve symptoms of catatonia, insomnia, autism severity, cognitive decline, and psychosis in Down syndrome disintegrative disorder.
Patient 4

Patient 4 was a 25-year-old male with mild intellectual disability, living independently when his decline began. He had a prodrome of malaise, joint pain, and a sore throat. There was no apparent psychosocial stressor. Nine weeks later he developed acute psychosis over a 24-hour period, characterized by hallucinations and catatonia. At his worst, his family reported severe insomnia, catatonia, increased autistic features, incontinence, and headaches. MRI and cerebrospinal fluid studies were normal; however, he had antistriational and celiac antibodies. He was treated for Celiac disease by a gastroenterologist.

His catatonia was partially responsive to benzodiazepines. IVIG led to resolution of hallucinations and catatonic symptoms and moderate improvement in mood and social interactions, but not insomnia. He never received steroids. After changing from sertraline to fluoxetine he had further improvement and is now symptom free.

DISCUSSION

All patients had DSDD, with cognitive decline, new or worsening autistic features, and insomnia. Consistent with descriptions by Ghaziuddin et al. and Jacobs et al., catatonia was common to all as well and is now included in the clinical features of DSDD. Three patients developed psychosis and one had seizures. There was no report of newly diagnosed sleep apnea surrounding the onset of symptoms in any case. All patients in this study had documented auto-antibodies (Table I), experienced acute to subacute onset of symptoms in late adolescence or young adulthood, and were treated with immunotherapy within 6 months (Table II). Evaluations, including MRI,
electroencephalography, and serum and cerebrospinal fluid studies, were negative except as noted in Table I. There was otherwise no evidence of inflammation in any patient. All four patients had improvement in overall function as well as in all above-mentioned symptom domains within weeks after immunotherapy, compared with the reported natural history of slow but incomplete improvement over the course of years.

Previously, patients with Down syndrome and such an encephalopathy may have been misdiagnosed as having early-onset Alzheimer disease. More recently, however, these symptoms have become recognized as a separate disease entity.6–8 Various etiologies have been proposed for the common phenotype of DSDD. Mircher et al.8 found most patients had a triggering stressor before the onset of symptoms. Similarly, Stein et al.7 associated the symptoms of DSDD with stress and anxiety. Capone et al.9 attributed similar symptoms to depression and obstructive sleep apnea. A psychosocial stressor was identified in two of our patients. That these two patients improved after immunotherapy suggests immune dysregulation may also have played a role in their disintegration.

While new onset encephalopathy can be due to autoimmune encephalitis, none of the patients in this study would have met criteria for autoimmune encephalitis.10 Our study shows, however, that patients with DSDD and evidence of autoimmunity may also respond to immunotherapy, improving much more rapidly than the natural history of DSDD.1

Although all four patients had a history of autoimmunity, active, detectable autoimmunity does not appear to be required for DSDD, nor does it predict response to immunotherapy. Patient 1 was actually seronegative at the onset of DSDD symptoms but had the most robust response to immunotherapy. Rather, these patients may have a dysregulated immune system which predisposed them to both autoimmune disease and encephalopathy.

One patient had a marked response to the combination of ECT and immunotherapy in both aggression and cognition. The patients with probable DSDD presented by Ghaziuddin et al.2 all responded to ECT. ECT has been used successfully to treat the catatonia of N-methyl-D-aspartate receptor encephalitis11,12 and aggression in children with autism.13 However, ECT requires conscious sedation or anesthesia, patients may need many sessions, and it is associated with memory and cognitive impairment.14 Immunotherapy, by contrast, is less invasive and has fewer permanent side effects. It may be that for some patients, ECT and immunotherapy are complimentary.

Our study has limitations. It is a small case series, but it introduces a new approach to treating selected patients. It depended on parent recall, sometimes of events in the relatively distant past. Often parents recalled that symptoms were worse than physicians perceived at the time because of behavioral issues. Because patients did not have symptoms of sleep apnea, sleep studies were not performed and this comorbid diagnosis may have been missed. Finally, immunotherapy regimens were too varied to draw generalizable conclusions, but our experience suggests that steroids and IVIG should be the cornerstone of treatment.

In conclusion, immunotherapy may be of benefit to some patients with DSDD, but further prospective study is recommended to clarify response and selection of immunotherapy candidates.

ACKNOWLEDGEMENTS
We are grateful to the Anna’s Angels Foundation for their ongoing support of the Duke Comprehensive Down Syndrome clinic and research program, including support for our research on Down syndrome disintegrative disorder. The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

SUPPORTING INFORMATION
The following additional material may be found online:
Table SI: Rating scale scores and autism severity for each patient at each time point
REFERENCES


