CLINICAL REPORT

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Rapid Clinical Deterioration in an Individual with Down Syndrome

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A small percentage of adolescents and young adults with Down syndrome experience a rapid and unexplained deterioration in cognitive, adaptive, and behavioral functioning. Currently, there is no standardized work-up available to evaluate these patients or treat them. Their decline typically involves intellectual deterioration, a loss of skills of daily living, and prominent behavioral changes. Certain cases follow significant life events such as completion of secondary school with friends who proceed on to college or employment beyond the individual with DS. Others develop this condition seemingly unprovoked. Increased attention in the medical community to clinical deterioration in adolescents and young adults with Down syndrome could provide a framework for improved diagnosis, evaluation, and treatment. This report presents a young adult male with Down syndrome who experienced severe and unexplained clinical deterioration, highlighting specific challenges in the systematic evaluation and treatment of these patients.

Key words: Down syndrome; catatonia; regression; psychosis

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INTRODUCTION

In recent years, a small number of providers have described young adults with Down syndrome (DS) who abruptly deviated from their normal developmental trajectory and experienced unexplained, rapid clinical deterioration. Some are referring to this condition as "Down Syndrome Disintegrative Disorder," [Prasher, 2002; Devenny and Matthews, 2011; Worley et al., 2014] "New-onset Autistic Regression," [Worley et al., 2014] "Catatonic Psychosis," [Rollin, 1946] "Acute Regression of DS," [Akahoshi et al., 2012] or "Catatonia in DS" [Ghaziuddin et al., 2015]. This sudden process often involves loss of daily living skills, cognitive decline, psychomotor slowing, disordered sleep, loss of speech, unintentional weight loss, uncharacteristic anxiety, depression and/or mood lability, and new-onset or worsening repetitive thoughts and behaviors [Prasher, 2002; Devenny and Matthews, 2011; Worley et al., 2014]. In some cases, patients experience aggression toward others, apparent psychosis, or signs of catatonia [Devenny and Matthews, 2011]. Unclear is whether stressful experiences (such as the death of a loved one) or transitional life events (such as graduation from high school) are precipitants. Alzheimer's disease is unlikely to present in patients with DS younger than 35 years [Moran et al., 2013]; this subset of patients with clinical decline demonstrates different and more rapid deterioration.

This clinical presentation leaves providers without a systematic means of diagnosis, evaluation, and treatment of these patients. These young adults and their loved ones therefore traverse an untried path of complex diagnostic studies, psychopharmacology, and other treatment interventions. An established algorithm for care would bring improved efficiency and consistency to this process and facilitate comparison across treatment centers to enhance our understanding of the etiology and management of this condition. The following clinical report highlights the challenges these individuals face, demonstrates an approach to their care, and reveals treatments that have shown some success at our Program.

Abbreviations: DS, Down syndrome; ADHD, attention deficit hyperactivity disorder.

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CLINICAL REPORT

A 19-year-old man with DS presented with 1.5 years of clinical deterioration, including a precipitous loss of functioning over the previous 2 months. His most notable changes included probable psychotic symptoms, staring episodes, loss of speech and written expression, and decreased ability to execute activities of daily living, despite numerous trials of antidepressant and antipsychotic medications, alone and in combination.

Prior to age 12 years, his medical history was significant for recurrent otitis media, myopia, constipation, and adenoid and tonsillar hypertrophy. He had tympanostomy tubes placed three times, and he now wears hearing aids bilaterally for sensorineural hearing loss. He wears eyeglasses to correct myopia and takes a daily medication for chronic constipation. He had an adenotonsillectomy with residual mild obstructive sleep apnea, treated with continuous positive airway pressure (CPAP).

At age 12 years, he was diagnosed with ADHD and treated separately at various times with methylphenidate, combined amphetamine and dextroamphetamine, and atomoxetine. All were ultimately discontinued due to side effects including tearfulness, agitation, tics, and difficulty with sleep. Continued ADHD symptoms were treated with guanfacine and venlafaxine. These were ultimately discontinued due to side effects and lack of improvement. He was also treated for mild depression and showed some improvement in symptoms on citalopram 10 mg per day, but this was also discontinued because his parents felt he was doing well without it.

Starting at age 14, his mother reported that he had intrusive, repetitive thoughts about television shows, which alternated between comforting and anxiety-provoking depending on the content of the shows. These thoughts, as well as moderate symptoms of depression, were unimproved following adequate trials of fluvoxamine and fluoxetine. Further evaluation at this time showed normal thyroid stimulating hormone (TSH), free thyroxine (fT4), hemoglobin, hemoglobin A1c, cholesterol, celiac disease screen, and X-ray of the cervical spine.

He began to show deterioration in function at 17.5 years of age following graduation from high school. Prior to his clinical decline, he was happy and successful in a full inclusion program from elementary school through high school. His parents described his high school experience as "seamless and full of activity and proper supports."

In the 2 months prior to visiting our clinic, he declined dramatically. His mother reported that he had "a sad affect, difficulty organizing his thoughts and concentrating, a paucity of thought, fretfulness around doing the right thing and not wanting to disappoint others, and feeling guilty that he is ruining things." He expressed concern about "growing up." He also began to move slowly, talk to himself, repeatedly zip and unzip his jacket, shift his cell phone from one pocket to the other, and change his seat often. He began to speak incoherently in one-word responses and developed difficulty writing. His mother also reported episodes where she found him staring and "frozen in odd positions, clearly tormented," sometimes in the bathroom or the shower, and had to physically move him. In other situations, his eyes darted around the room while he searched to answer a question. He began to wave to empty spaces, put his fingers in his ears and close his eyes, and mentioned hearing voices but would not say what the voices told him. He had difficulty sleeping, experienced a loss of appetite, and lost eight pounds within a year. During this same year, his sister returned to college, and his favorite character from a television show died both on the show and in real life.

When he visited our Program, his parents were distressed about his accelerated clinical decline and behavioral changes. Our initial differential diagnosis included pathology that causes or might worsen subacute psychiatric symptoms in young adults with an emphasis on those that are more prevalent in people with Down syndrome. This included worsening hearing loss, vision changes, diabetes mellitus type 1, untreated obstructive sleep apnea, hyperthyroidism, hypothyroidism, celiac disease, and blood disorders. We also considered the more common causes of subacute psychiatric changes in young adults in the general population including electrolyte disturbance, Lyme disease, HIV, seizure disorder, brain tumors, and N-methyl-D-aspartate (NMDA) receptor encephalitis. He had recent normal hearing and vision evaluations and was using his CPAP regularly. Our laboratory workup revealed a normal hemoglobin A1c, TSH, fT4, anti-thyroperoxidase antibodies (TPO), anti-thyroglobulin antibodies (TGA), IgA anti-tissue transglutaminase (TTG) antibody, complete blood count (CBC), Chem 7, Lyme antibodies, HIV viral load, electroencephalogram, brain MRI, spinal MRI, and testicular ultrasound.

Following an unrevealing initial workup, we chose to pursue testing for less common causes of subacute psychiatric deterioration in young adults. This workup revealed normal erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Vitamin B12, folate, homocysteine, antinuclear antibody (ANA), liver function tests (LFTs), cholesterol panel, rapid plasma reagin (RPR), chromosomal microarray, Fragile X syndrome testing, plasma amino acids, plasma acylcarnitines, urine organic acids, urine acylglycines, pyruvate, lactate, ammonia, NMDA receptor autoantibody test, Cytochrome P450 2D6 testing, and serum manganese, nickel, zinc, thallium, mercury, and lead levels. He had low copper and ceruloplasmin levels; however, his 24-hr urine copper test for Wilson's disease was normal. He was treated for a low 25-OH Vitamin D level. He also had a normal echocardiogram.

Concurrent to this workup, we referred him to a psychiatrist who specializes in treating individuals with neuropsychiatric and neurodevelopmental disorders across the lifespan. He was diagnosed with a single major depressive episode, severe, with probable psychotic features, and catatonia. Different psychopharmacologic trials, which were discontinued due to undesirable outcomes, included (i) bupropion and trazodone (for disturbed sleep) along with olanzapine, aripiprazole, and ziprasidone which were added individually and sequentially; (ii) lithium and trazodone; and (iii) high dose lorazepam up to 14 mg/day and trazodone. The treatment team felt that olanzapine, aripiprazole, and ziprasidone exacerbated his catatonia and overall decline. He remained agitated, tearful, psychotic, and paranoid on lithium and lost his ability to complete all activities of daily living. He did not improve significantly with high-dose lorazepam. Electroconvulsive therapy (ECT) was considered but not pursued.

His current pharmacologic treatment includes clozapine 175 mg daily. On this regimen, his mother reports that he is about 85%

TABLE I. Systematic Approach to Evaluating Clinical Deterioration in Individuals With Down Syndrome

Evaluation	Diagnosis
Tier 1	
Thyroid stimulating hormone, free T4, thyroid peroxidase, thyroglobulin antibodies	Hypothyroidism, hyperthyroidism, Hashimoto's encephalopathy
Electrolytes, complete blood count with differential, liver function tests	Electrolyte disturbance, infection, liver disease
Folate, Vitamin B12, 25-OH Vitamin D	Vitamin deficiency
Homocysteine	Homocystinuria
Tissue transglutaminase-IgA, total IgA	Celiac disease
Polysomnogram	Obstructive sleep apnea
Hearing test	Hearing loss
Vision screen	Cataracts, Ulcer etc.
Abdominal X-ray	Constipation
Depression screen	Depression
Screen for stressors	Stress and generalized anxiety disorder
Psychiatry referral	Psychiatric disorder
Brain MRI (severe presentation or symptoms lasting >6 mos)	Brain abnormality
Tier 2	
Lyme antibodies	Lyme disease
Anti-streptolysin O (positive strep <6 months ago) and now having tics, obsessive-compulsive symptoms, other abnormal movements	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
Electroencephalogram	Seizure disorder
Antinuclear antibodies, erythrocyte sedimentation rate, and C-reactive protein	Rheumatologic/Immunologic disorder
Rapid plasma reagin, human immunodeficiency virus viral load, if sexually active	Syphilis, human immunodeficiency virus
Tier 3	
Fragile X syndrome testing	Fragile X syndrome
Methyl CpG binding protein 2 (MECP2), if female	Rett syndrome
Lead, manganese, mercury, zinc, nickel, thallium	Heavy metal toxicity
Anti-N-methyl D-aspartate receptor autoantibodies	N-methyl D-aspartate receptor Encephalitis
Chromosomal microarray	Microdeletion/Microduplication syndrome
Tier 4	
Plasma amino acids	Aminoacidopathies
Urine organic acids	Organic acidurias
Urine acylglycines	Organic acidurias
Plasma acylcarnitines	Fatty acid oxidation disorders
Pyruvate	Mitochondrial disorders
Lactate	Mitochondrial disorders
Ammonia	Urea cycle disorders
Ovarian ultrasound	Ovarian teratoma (Limbic encephalitis)
Tier 5	
Whole exome sequencing	Genetic disorder
Urine glycosaminoglycans, Urine oligosaccharides, Urine sialic acid	Lysosomal storage disorders
Very long chain fatty acids, Phytanic acid, Plasmalogens	Peroxisomal storage disorders
Carbohydrate deficient transferrin	Congenital disorders of glycosylation
Aminolevulinic acid, porphobilinogen, hydroxymethylbilane synthase gene mutation	Porphyria
Hypoxanthine-guanine phosphoribosyl transferase gene mutation	Lesch–Nyhan syndrome

Tiers 3–5 test are for rare conditions and conditions that can appear in childhood (low yield).

back to his baseline level of functioning. He has returned to many community based-activities including paid employment, volunteer work, and numerous social activities, such as Special Olympics. Adverse effects from this medication include a 28-pound weight gain, sedation, and poor oral motor control, which makes articulation difficult. His white blood cell count and absolute neutrophil count have remained within normal limits.

DISCUSSION

This clinical report highlights the challenges involved in diagnosing, evaluating, and treating patients with DS who have experienced this rapid, unexplained clinical deterioration. Healthcare providers, including experts on DS, are working to develop diagnostic criteria for this clinical presentation [Down Syndrome Medical Interest Group USA]. In this clinical report, we describe one out of the 10 patients with this clinical presentation that we follow in our Program. They all share the following characteristics:

- Significant and precipitous loss of activities of daily living and baseline skills within 6 months
- Perceived decline in cognition
- Unexplained decompensation in behavioral functioning and mood
- Significant loss of speech
- Ages 10–30 years and usually post-pubertal at the time of onset
- Prior to onset, no history of autism spectrum disorder, infantile spasms, seizure disorder, or significant psychopathology.

To ensure that a patient with DS did not have an identifiable organic cause for their symptoms, we have applied a tiered series of tests that we assembled based on our review of the literature and communication with experts in the field (Table I). Many of our patients had positive results during their medical evaluation; however, treatment of these conditions did not lead to resolution of their deterioration. Laboratory testing beyond the first tier should be reserved for cases where first-tier diagnoses have been ruled out and there is still clinical suspicion for an organic etiology of neuropsychiatric disease. Medical costs should also be carefully considered in clinical decision-making. At the present time, there is no known consistently effective treatment for this type of clinical deterioration in patients with DS; however, certain pharmacological approaches have shown some promise. The literature indicates that high-dose benzodiazepine administration, such as lorazepam, may be helpful in patients with catatonia [Ghaziuddin et al., 2015]. Additionally, some patients with catatonia have benefited from ECT [Ghaziuddin et al., 2015]. Collaboration among healthcare providers by adding clinical reports, diagnostic evaluation, and treatment to the scant literature, is crucial to improving outcomes for these patients.

CONFLICTS OF INTEREST

Brian G. Skotko serves in a non-paid capacity on the Board of Directors or Scientific Advisory Boards for the Massachusetts Down Syndrome Congress, Band of Angels Foundation, and the National Center for Prenatal and Postnatal Down Syndrome Resources, all non-profit organizations. Dr. Skotko is the Co-Director of the Massachusetts General Hospital Down Syndrome Program and occasionally gets remunerated from Down syndrome non-profit organizations for speaking engagements about Down syndrome. He receives support for clinical drug trials involving people with Down syndrome from Hoffmann-La Roche, Inc. He has a sister with Down syndrome. Dr. Schwartz serves in a non-paid capacity on the Medical Scientific Advisory Board for the Massachusetts Down Syndrome Congress. She is also the Co-Director of the Massachusetts General Hospital Down Syndrome Program. Dr. McDougle and Julia Jacobs have no conflicts of interest to report.

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