

Down Syndrome Disintegrative Disorder: New-Onset Autistic Regression, Dementia, and Insomnia in Older Children and Adolescents With Down Syndrome

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Abstract

Over a 10-year period in a Down syndrome Clinic, 11 children and adolescents were encountered with a history of new-onset (8) or worsening (3) autistic characteristics. Ten of the 11 (91%) had cognitive decline to a dementia-like state and 9 of the 11 (82%) new-onset insomnia. The mean age at which symptoms developed was 11.4 years (standard deviation = 3.6 years; range 5-14 years), an older age than usual for autistic regression in Down syndrome. Ten of 11 cases (91%) had elevated (“positive”) thyroperoxidase antibody titers compared to only 5 of 21 (23%) age-matched control subjects with Down syndrome ($P < .001$). At follow-up at a mean age of 20.7 years (standard deviation = 3.9 years), 8 of the 11 (73%) were at least somewhat better. Down syndrome disintegrative disorder seems an appropriate name for this newly recognized clinical association, which may be due to autoimmunity.

Keywords

Down syndrome, disintegrative disorder, Hashimoto, insomnia, autism, thyroperoxidase antibody, catatonia

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The first case of autistic regression, cognitive decline, and insomnia was recognized in our Down syndrome clinic in 2002. Ten other similar cases were encountered over the next 10 years in a busy Down syndrome clinic with 2 attending physicians.

Autism is characterized by qualitative impairments in communication and in reciprocal social skills, along with restricted interests and repetitive routines or movements. Using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition–Revised*, criteria, Capone et al¹ found a Down syndrome clinic prevalence of Autism Spectrum Disorders of 13%. Castillo et al² studied regression among autistic children with Down syndrome, comparing it to regression in autistic children without Down syndrome. They found that 12 of 24 (50%) of the children with autism in their Down syndrome clinic had a history of loss of previously acquired language and sociocommunicative skills. The mean age at language loss in these children was 62 months, compared to 20 months in children with autism but without Down syndrome who also had had autistic regression.

Disintegrative disorder is a condition among the Pervasive Developmental Disorders of Childhood in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition–Revised*. It is characterized by the development of autism

and of cognitive deterioration in a previously typical child, occurring at an age that is higher than usual for autistic regression. For the diagnosis of disintegrative disorder to be made, there must have been at least 2 years of normal development followed by autistic regression; the regression must happen at age less than 10 years; and the regression must not be accounted for by another, more specific diagnosis. Disintegrative disorder is rare. A metabolic or autoimmune etiology is usually not found. Disintegrative disorder has been reported before in Down syndrome. Kerbeshian and Burd³ described an 8-year-old girl who developed new-onset insomnia and autism, and who also lost cognitive capabilities. Prasher,⁴ in a letter to the editor, reported that a “significant minority of

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young adults between the ages of 15 and 30 [with DS]... present with a specific regressive/disintegrative disorder" that is "gradual but severe," characterized by cognitive regression, language regression, loss of adaptive and social skills, and a change in behavior. No "precise cause" could be found.

Methods

This study was approved by the Duke University Medical Center institutional review board. Consent for participation was obtained from parents.

All cases were evaluated by one neurodevelopmental pediatrician (GW). To be included in the series, a case had to have had autistic regression and to meet *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition–Revised* criteria for the diagnosis of Autistic Disorder, not for Pervasive Developmental Disorder–Not Otherwise Specified. It was also necessary for a patient to be older than the usual age for autistic regression in Down syndrome (5 years or older).² Parents or caregivers were given a standard interview for autistic characteristics based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria. It also was necessary for a case to have developed at least 6 *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition–Revised*, diagnostic criteria, the same number of criteria as is required for the diagnosis of autism in other children. For children with Down syndrome who had autism before regression, autistic regression needed to have occurred also in at least 6 diagnostic criteria.

A history for cognitive decline to a dementia-like state was carefully elicited from parents for all cases. It was taken by developmental domain (cognitive development; language development; fine motor development; gross motor development; and the development of skills of daily living). Using a standard interview format, capabilities and achievements at the time of the initial evaluation in the Duke DS Clinic were contrasted to the case's condition before deterioration began. Parents were asked to bring to a subsequent visit school records and examples of school work before and after the decline to substantiate the history they gave of their child's deterioration. Psychometric testing before and after the decline was not available for any patient and psychometric testing was not done in the Duke DS Clinic. Histories of insomnia and of seizures before and after deterioration were specifically elicited. Detailed histories of cognitive decline and of the development of new autistic symptoms were retaken at second and subsequent visits in 10 of 11 cases and in the other case, with institutional review board approval, by phone interview, and all initial histories were confirmed.

Serum samples from all cases and controls were analyzed for thyroperoxidase seropositivity by the Duke University Medical Center Clinical Laboratories, using standard technique.⁵ Control samples were selected from the "Duke Down Syndrome Bio-Bank," an institutional review board–approved repository of serum samples from subjects with Down syndrome who were recruited from the Duke DS Clinic. Control samples were matched to cases at a ratio of 2 controls to 1 case. Controls were chosen to be up to 6 months younger to any age older than cases, because older age is associated with a higher rate of thyroperoxidase antibody seropositivity.⁶ Having controls older than cases would make it more difficult statistically to establish a higher rate of thyroperoxidase seropositivity in cases than in controls.

Table 1. Clinical Characteristics of Cases When First Evaluated in the Down Syndrome Clinic (n = 11).

Characteristics	Number	Percent (%)
Autistic deterioration	11	100
Cognitive decline (dementia-like state)	10	91
New-onset insomnia	9	82
Hallucinations	1	9
Seizure disorder	1	9
Treated hypothyroidism	5	45

Statistical Analyses

For cases, descriptive statistics were produced for age at diagnosis, age of reported onset of symptoms, and age at last follow-up visit when outcome was determined. For control subjects from the Down Syndrome Bio-Bank, descriptive statistics were produced for age at enrollment when blood was obtained for the repository. Two-sided Fisher exact tests were used to investigate the association of exposures (cases vs controls) and seropositivity for thyroperoxidase and for treated thyroid disease.

Student *t* test was used to test the hypothesis that there was a significant difference between cases and controls for age at which blood was obtained for analysis for thyroperoxidase antibody titer.

Results

Eleven cases meeting inclusion criteria were encountered between 2002 and 2011. Cases were first seen in the Duke DS Clinic at a mean age of 14.8 years (standard deviation = 2.7). Autistic regression was reported by parents to have begun at a mean age of 11.4 years (standard deviation = 3.6) (range = 5–14 years), a mean of 3.4 years before patients were first seen in the Duke DS Clinic. Nine of 11 (82%) were 10 years old or older at the time their condition deteriorated and 2 of 11 (18%) were younger (5 and 6 years, respectively). The sex ratio was 7 girls (64%) to 4 boys.

Table 1 presents the clinical characteristics of cases when first seen in the Down syndrome clinic. All 11 cases (100%) met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition–Revised*, criteria for the diagnosis of autism. Eight of 11 (73%) were not autistic before their autistic regression. Three (27%) were autistic, but their autism worsened in 6 *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition–Revised*, autistic disorder diagnostic criteria or more. New onset insomnia was defined by parents as their children getting very little sleep day or night and being constantly fatigued when awake. It was present in 9 of 11 (82%) cases.

Table 2 presents the laboratory evaluation undertaken at the Duke University Medical Center or elsewhere (for most cases, records from other hospitals were incomplete). One case (9%) developed celiac disease and 10 had persistently negative tissue transglutaminase antibody titers. Other negative diagnostic studies included negative antinuclear titers, anti-streptolysin O antibody titers, and anti-DNase B antibody titers and normal erythrocyte sedimentation rates and C-reactive

Table 2. Laboratory Evaluation; n = 11.

Test	Number (%)	Results
Brain imaging (CT or MRI)	7 (64)	Normal
Metabolic workup	9 (82)	Normal
EEG	1 (9)	Seizure disorder

Abbreviations: CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging.

Table 3. Condition at Follow-Up.

Condition	Number (%)
Worse	0 (0)
No change	3 (27)
Better	8 (73)
Relapses	0 (0)

protein titers. In cases encountered later in the series, studies obtained depended on the duration of Down syndrome disintegrative disorder symptoms before presentation to the Down syndrome clinic, and the history and examination at the first visit. Some patients had only thyroid antibody studies done.

Follow-up of the 11 cases is presented in Table 3. The mean age at follow-up was at 20.7 years (standard deviation = 3.9, range = 13-25 years), at a mean of 9.2 years after symptoms developed and a mean of 5.9 years since they were first seen in the Down syndrome clinic. There was gradual clinical improvement in most cases (8/11; 73%), but only 1 case returned to his pre-deterioration condition, a case with autism beforehand. There have been no relapses to date.

Two cases were treated with steroids late after presentation and neither improved.

Thyroid Autoimmunity

All cases had thyroid autoimmunity: 9 of 11 (82%) had thyroperoxidase seropositivity at the first visit; 1 case (9%) initially had an intermediate thyroperoxidase antibody titer that became seropositive later; and 1 case (9%) developed the anti-thyroid-stimulating hormone receptor antibody associated with new-onset Graves disease subsequently but never became thyroperoxidase seropositive.

Five of 11 (45%) were treated for thyroid disease (hypothyroidism) when first seen, increasing over the 5.9-year follow-up period to 9 of 11 (82%; $P = ns$), of whom 8 were treated for hypothyroidism and 1 for Graves disease. All patients were euthyroid on treatment.

Twenty-one control subjects without autism were selected from the Duke Down Syndrome Bio-Bank. The mean age of control subjects was 18.7 (standard deviation = 3.7) years. This was significantly older than the mean age at which cases were first seen in the Down syndrome clinic (14.8; standard deviation = 3.9 years; $P < .01$). Fewer controls were females

(9/21; 43%) than in cases, but the difference was not significant (7/11; 63%). The rate of thyroperoxidase seropositivity for controls was 5/21 (23%). The rate of thyroperoxidase seropositivity was greater in cases (10/11; 91%) than in controls (5/21; 23%; $P < .001$).

Discussion

Down syndrome disintegrative disorder seems an appropriate name for this condition. Down syndrome disintegrative disorder shares with disintegrative disorder in typical children all essential clinical characteristics:

1. Autistic regression;
2. Cognitive decline resulting in a dementia-like state;
3. Occurrence at an older age than usual for autistic regression;
4. No other diagnosis established that could explain the condition.

There are 3 arguments for Down syndrome disintegrative disorder being different from the autistic regression in children with Down syndrome reported by Castillo et al.² First, Down syndrome disintegrative disorder patients were older at age of deterioration. Nine of 11 (82%) Down syndrome disintegrative disorder patients were older than 10 years at the age of deterioration versus none of 9 (0%) in the case series of Castillo et al² ($P < .001$). Second, Down syndrome disintegrative disorder cases were predominantly female (7/11; 64%), compared to being predominantly male in children with Down syndrome and autistic regression (9/12; 75%; $P = .07$). Third, new-onset insomnia was a striking feature of Down syndrome disintegrative disorder cases, volunteered by parents, but not commented upon by Castillo et al.²

The requirement for diagnosis of disintegrative disorder that the condition could not be attributed to another diagnosis was met in our Down syndrome disintegrative disorder cases, both by the negative workup done in some cases and by the absence of new symptoms or progression of any kind, which would have been likely if another underlying neurologic disease had caused the condition.

There was gradual improvement in the symptoms of most cases, but, except for 1 case with autism before regression who approached his pre-disintegration state, all were left with autism and with intellectual disability worse than before deterioration.

Insomnia was initially perceived by parents to be a severe problem, affecting their child's quality of life (and theirs). Of all Down syndrome disintegrative disorder clinical characteristics, it improved most frequently. No patient had a sleep study done.

No medication or combination of medications was consistently effective, but risperidone, fluoxetine, sertraline, trazodone, donepezil, and rivastigmine each helped at least 1 patient some. No particular medication can be recommended. The improvement in core symptoms experienced by 8 of 11 cases was mostly spontaneous, not due to an intervention.

Down syndrome disintegrative disorder was associated with thyroid autoimmunity. The prevalence of thyroperoxidase seropositivity was significantly greater in cases than in controls from our Down Syndrome Bio-Bank. Further, the prevalence of thyroperoxidase seropositivity in cases was significantly greater than that found in both of the case series in the literature that are appropriate for comparison: Ivarsson et al⁷ found that 13 of 30 patients (43%) with Down syndrome 12 to 19 years old had thyroperoxidase seropositivity compared to 10 of 11 (91%) in our series ($P < .05$). Gibson et al found that 8 of 101 patients (8%) 10 to 20 years old had thyroperoxidase seropositivity,⁸ also less than the 91% in our cases ($P < .001$). All cases with Down syndrome disintegrative disorder in our series had thyroid autoimmunity on at least 1 test, either when first seen or at some time during the follow-up period (2 cases). Finally, the rate of treated thyroid disease (9/11; 82%) in our cases at follow-up at a mean age of 20.7 years was greater than the rate of treated thyroid disease in 20-year-old patients reported in the literature in 1998 by Karlsson et al⁶ (28/85; 33%; $P \leq .003$).

Waternberg et al⁹ defined Hashimoto encephalopathy as “a syndrome of persisting neurological and neuropsychological deficits with elevated titers of antithyroid antibodies in individuals who were usually euthyroid or only mildly hypothyroid.” It is rare in childhood. Alink et al¹⁰ reviewed 25 cases. The median age at presentation was 14 years. The most frequent clinical symptoms were seizures (80%), confusion (52%), headache (40%), hallucination (32%), and ataxia (36%). These symptoms were not found in our cases of Down syndrome disintegrative disorder. Nonetheless, acute psychiatric illness as the predominant symptom of Hashimoto encephalopathy has been reported.¹¹ Hashimoto encephalopathy has been reported in 2 adults with Down syndrome¹² and in 1 adolescent with Down syndrome.¹³

Thyroperoxidase seropositivity is thought to be more specific for the diagnosis of Hashimoto encephalopathy than in seropositivity for other thyroid antibodies.^{14,15} Whether thyroperoxidase antibodies are pathogenic or only a parameter for other pathogenic antibodies is an unsettled issue.^{12,13} Helene et al¹³ found antibodies against dimethylargininase-1 in a 15-year-old girl with Down syndrome and cognitive decline, also a possible case of Down syndrome disintegrative disorder.

A differential diagnosis includes Alzheimer disease, but the improvement in the clinical condition in most cases at follow-up, the younger age at onset of deterioration in Down syndrome disintegrative disorder than in Alzheimer disease in Down syndrome,¹⁶ and the history of acute or subacute deterioration, not the more gradual decline of Alzheimer disease, all argue against Alzheimer disease as the cause of Down syndrome disintegrative disorder. We did not measure β -amyloid in cerebrospinal fluid or in serum.

Depression is another possible cause of intellectual and adaptive decline in our cases. Capone et al¹⁷ reported on 28 adolescents and young adults who met diagnostic criteria for a major depressive episode. Of these, functional decline was reported in 19 (68%), to compare to none of the controls

with Down syndrome. Twenty-four (86%) of the cases had obstructive sleep apnea syndrome, compared to 44% of controls. There was overlap in symptoms between their cases and ours. Compared to their controls, their cases more frequently had autism and stereotypy. Results of treatment of sleep apnea were not reported. It is therefore not possible to know if the sleep apnea was a primary cause of the depression.

A systematic history for depression was not elicited for our 11 cases. This remains a possibility, but the severity of decline, the lack of sadness in our cases, and the lack of dramatic response to pharmacological treatment suggest that our cases of Down syndrome disintegrative disorder may have been different from those of Capone et al.¹⁷

Another diagnostic possibility is new-onset catatonia. Jap and Ghaziuddin¹⁸ reported 2 adolescent females with Down syndrome who developed subacute social withdrawal, stereotypic movements, rigidity, and posturing. One had preexisting Pervasive Developmental Disorder–Not Otherwise Specified. One responded to lorazepam and fluoxetine in combination and the other to electroconvulsive therapy. Wing and Shah¹⁹ described the development of catatonia in 30 individuals with Autistic spectrum disorders, 6% of all patients with autism referred to them. Their “essential criteria” for diagnosis of catatonia were slowness, difficulty initiating movements, and/or passivity. The majority of cases were 10 to 19 years old at presentation. They comment that “there is a marked overlap of behavioral features” between autism and catatonia, including “motor stereotypies, mannerisms, rituals, mutism, echolalia, and negativism, among others.” The key clinical features differentiating catatonia and autism were “an odd gait, odd stiff postures, and freezing” in the context of the above “essential criteria.” We did not evaluate our cases for these diagnostic criteria and cannot comment on whether or not they were present. The response to electroconvulsive therapy in one patient and lorazepam and fluoxetine in the other presented by Jap and Ghaziuddin¹⁸ suggest that these treatments ought to be considered in patients who have features of catatonia associated with Down syndrome disintegrative disorder. No case in our series had either treatment.

No case developed any new sign or symptom suggestive of an underlying neurologic diagnosis; no child developed seizures making epileptic encephalopathy an unlikely primary diagnosis, no child had a new focal neurologic finding suggestive of a central nervous system vasculitis, and no child had celiac disease. No explanatory diagnosis was made by any other physician who saw cases during the follow-up period.

We speculate that it is possible that some of the cases of autistic deterioration in younger children, such as those described by Castillo et al,² might also be due to Down syndrome disintegrative disorder, because the youngest child with Hashimoto encephalopathy reported in the literature was 2 years 10 months at presentation.²⁰ Because treatment with steroids and/or intravenous immunoglobulin can improve outcome in some patients with Hashimoto encephalopathy if given promptly after onset, it is possible that early treatment of Down syndrome disintegrative disorder with thyroperoxidase

seropositivity might also be effective. This, of course, would depend on early recognition of the condition. The only 2 cases in our series who received steroids had no response to them.

We acknowledge that there are limitations to our study. Although a consistent history was obtained and consistent physical examination done, the diagnoses of autistic regression and of cognitive decline were dependent on parents reporting their child's condition before deteriorating, which happened at a mean of 3.4 years prior to when first seen in the Duke DS Clinic. No pre- or postdeterioration testing was done and no independent verification of the parental history of decline was obtained. Standardized tests for the diagnoses of autism and intellectual disability were not done, but repeated visits of children allowed for verification of the initial history, reaffirming thereby the diagnoses of autism and new-onset cognitive decline made by a standard interview. Finally, there might have been a referral in favor of cases with thyroperoxidase seropositivity, because the parents of previously diagnosed children recruited other similar children for referral to our clinic, using thyroperoxidase seropositivity as one reason to send us patients.

Down syndrome disintegrative disorder is an umbrella term that could cover an autoimmune condition, a major depressive episode associated with sleep apnea, and new-onset catatonia. These diagnoses may not be mutually exclusive either. Because the clinical deterioration is calamitous in all 3 conditions, prudence dictates that patients should be evaluated for each of them and appropriate treatments initiated.

In conclusion, Down syndrome disintegrative disorder seems an appropriate name for this rare disorder. We found that it was associated with thyroid autoimmunity, suggestive of it being of autoimmune etiology.

Author Note

This work was presented at the "Festschrift for Dr. Gregory S. Liptak," at the Golisano Children's Hospital, Upstate Medical Center, Syracuse, New York, on March 24, 2012, and is dedicated to the memory of this good man. It was also presented at the Down Syndrome Medical Interest Group Meeting, Denver, Colorado, on July 20, 2013.

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Author Contributions

GW and PSK collected together the case series. GW interviewed all patients twice and wrote the first draft of the manuscript. BGS handled IRB issues. GW, CM, and DWA collected and collated data. EC performed the thyroperoxidase antibody measurements.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study and the Down Syndrome Bio-bank were approved by the Duke University Medical Center Institutional Review Board.

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