Is Developmental Regression in Down Syndrome Linked to Life Stressors?

Sabrina Sargado, MD,*† Anna L. Milliken, BA,* Margaret A. Hojlo, BA,* Katherine G. Pawlowski, BA,* Diana Deister, MS, MD,*†‡ Cara N. Soccorso, PsyD,*† Nicole T. Baumer, MD, MEd*†§

ABSTRACT: ***Objective:*** **Unexplained regression in Down syndrome (URDS) involves a loss of acquired skills resulting in functional deterioration. Despite extensive workup and treatment, few individuals regain baseline function. This study aimed to understand the role of psychosocial stressors in URDS.** ***Methods:*** **We describe psychosocial stressors in 14 cases of URDS. Specifically, we examined psychosocial stressors in the context of presentation and clinical symptoms. We also examined co-occurring neurodevelopmental disorders and medical and mental health conditions.** ***Results:*** **All individuals experienced psychosocial stressors within one year of diagnosis of URDS. The most common psychosocial stressors were moving to a new home or school.** ***Conclusion:*** **Psychosocial stressors are commonly reported preceding URDS. Knowledge about psychosocial stressors' impact may lead to preventive interventions, improved monitoring, and earlier diagnosis. Future research should focus on understanding psychosocial stressors to help identify individuals at risk for URDS and contribute to treatment.**

(*J Dev Behav Pediatr* 00:1–10, 2022) **Index terms:** Down syndrome, unexplained regression, psychosocial stressors, case series.

Down syndrome (DS), the most common chromosomal disorder, is a genetic condition caused by having a full or partial extra copy of chromosome 21.[1,2] An increasingly recognized phenomenon of unexplained regression occurs in individuals with DS (unexplained regression in Down syndrome [URDS]), particularly during adolescence, in which previously acquired skills are lost, resulting in functional deterioration (e.g., complete loss of toileting skills and loss of or decrease in use of language) that greatly affects quality of life, activity, and participation in the community.[3] URDS occurs without a clear, precipitating medical etiology. Manifestations of URDS may include loss of language, social withdrawal, personality, gross motor changes, a decline in activities of daily living (ADLs) such as toileting and feeding, sleep disturbance, an increase in stereotypies/abnormal movements, and an increase in aggressive behaviors.[4] Additional features may include psychosis and catatonia.[3,5]

From the *Division of Developmental Medicine, Boston Children's Hospital, Boston, MA; †Harvard Medical School, Boston, MA; ‡Department of Psychiatry & Behavioral Sciences, Boston Children's Hospital, Boston, MA; §Department of Neurology, Boston Children's Hospital, Boston, MA.

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Address for reprints: Sabrina Sargado, MD, Division of Developmental Medicine, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115; e-mail: sabrina.sargado@childrens.harvard.edu.

Patients with URDS undergo extensive clinical workup for contributing neurological causes, including seizures or structural brain anomalies, or other medical problems, such as thyroid disease or obstructive sleep apnea.[3,6,7] Workup for URDS has previously been found to be low yield, with abnormal measures that included sleep studies, blood work, and neuroimaging the same in cases of URDS and matched controls, suggesting that abnormalities identified were not the "sole cause of regression."[3]

There are currently multiple pathways to treatment that include patients receiving pharmacologic therapy (e.g., medications for anxiety and high-dose benzodiazepines to treat catatonia), immunotherapy (e.g., IVIG), and electroconvulsive therapy (ECT). Multimodal treatment is common.[5,8] In one study, despite extensive workup and multimodal treatment, a return to baseline functioning occurred in only 10% of individuals with DS who experienced regression; 46% did not recover, and 43% had partial recovery.[9]

The current research suggests that several factors may contribute to regression. Some individuals have had symptoms attributed to life events, trauma, or environmental changes.[6,9,10] In certain cases, medical conditions such as sleep apnea, Hashimoto disease, and depression were noticed in addition to psychosocial factors before regression.[9] Psychosocial stressors have recently gained ground as a possible contributing factor to URDS. Reports of significant life events or transitions often occur before regressive symptoms are noticed. Examples of stressful life events that have been reported include parental divorces, transitioning from high school to adult life, major surgeries, and family deaths.[5,9,11] When

compared with age-matched and sex-matched controls, individuals with URDS were found to have experienced more stressors and depressive symptoms.[3] The hypothesis that stressful life events may contribute to the presentation of URDS patients is of clinical importance and may influence diagnostic and treatment practices.

This research was conducted in the Boston Children's Hospital Down Syndrome Program (BCH DSP), a pediatric tertiary hospital. A group of multidisciplinary clinicians was created within the Down Syndrome Medical Interest Group in the United States in 2017, and an international consortium of DS clinics has shared data on cases of URDS. This group has focused on characterizing features, diagnosis, and treatment.[12] Our BCH DSP group joined the international consortium in 2019 and began collecting data as part of a large multisite study about URDS. Additional psychosocial data were collected for the subset of participants from our program.

Although previous research has looked at diagnostic evaluation and treatment in URDS, this study focused specifically on psychosocial stressors as a possible contributing factor to this entity. The aim of this case series was to explore the variety and potential impact of psychosocial stressors occurring in the year preceding the onset of URDS, in the context of other factors such as medical history, educational setting, and treatment.

METHODS

Patients

Patients consisted of individuals seen in the BCH DSP with diagnoses of DS and unexplained regression.

Patients were identified using a medical record query using *ICD* codes for regression and DS and who were seen in the BCH DSP in the last 10 years. Medical records were then reviewed. Individuals with no documented loss of skills were screened out. Regression stemming from purely behavioral challenges and those characterized as only involving speech and language skills were not included. The remaining patient records were reviewed for documented medical/neurodevelopmental etiology for their regression. Fourteen individuals were identified as having URDS (see Fig. 1).

Procedure

Institutional Review Board approval was obtained to conduct retrospective chart reviews. We conducted a retrospective chart review from electronic medical records of patients seen in the BCH DSP. Information was abstracted from BCH DSP clinic notes and a clinical database of caregiver and clinician-reported medical history, including regression symptoms, family and patient medical history, and psychosocial factors.

Sociodemographic information; medical, neurodevelopmental, and relevant family history; results of diagnostic workup; and the Bush-Francis Catatonia Scale (BFCS) scores were extracted from clinical notes by a research assistant (RA) and the principal investigator (PI). Diagnostic workup results that were collected through chart review included blood work, brain magnetic resonance imaging (brain MRI), electroencephalography (EEG), and sleep studies. The BFCS is a 23-item rating scale, with items 1 to 14 used as a screening tool. Items 1 to 14 are marked as absent (0) or present (3). The presence of two or more of the screening items for 24 hours or longer would meet the diagnostic criteria for catatonia. For severity, items 1 to 23 are rated using a scale of 0 to 3, and the score is the sum of responses of all the items. The higher the score, the higher the severity.[13] For specific individuals, their baseline score (preregression) and peak score (at the time of regression) were included. Socioeconomic status (SES) for all individuals was determined by median household income accessed using census data.[14]

Clinical presentation was characterized and abstracted using the 28-item list of core features proposed as a definition of URDS by the international consortium of DS clinics in 2017.[3] Interventions and response to treatment were tracked over time. In this study, to focus inquiry on the frequency and potential impact of psychosocial stressors, the clinical and research team developed a procedure to investigate and categorize psychosocial stressors.

The BCH DSP clinical team (which includes at least one clinician from the following practice areas: child psychiatry, psychology, developmental-behavioral pediatrics, neurodevelopmental disabilities, or pediatric nursing) determined key psychosocial stressors affecting preteens, adolescents, and young adults with URDS. By consensus, five areas of focus were identified: traumatic events, adolescent transitions, changes at home, changes at school, and changes in social relationships. The research team then collected information about the type and occurrence of psychosocial stressors from clinical notes. The RA/PI indicated whether the individual had documentation of any of the psychosocial stressors present within one year before the diagnosis of regression. The clinical team reviewed the cases to determine whether they meet criteria for regression and reviewed occurrence and type of psychosocial stressors. Data entry was reviewed and verified by the PI.

All study data were collected and managed using REDCap electronic data capture tools hosted at BCH.[15,16]

RESULTS

Fourteen individuals ranging in age from seven to 21 years (mean = 16, SD = 4) were identified. Fifty-seven percent of the cases were female (n = 8), whereas 43% were male (n = 6), and the sample was predominately White (79%, n = 11). Based on patients' zip code, median income quartiles were spread from low (n = 1), moderate (n = 4), and middle (n = 6) to upper (n = 3) quartiles (see Table 1).

There was variability in clinical symptoms during presentation that was described using the 28 features of URDS in the study by Santoro et al (2020) (see Table 2).[3] The onset of regression ranged from a subacute process

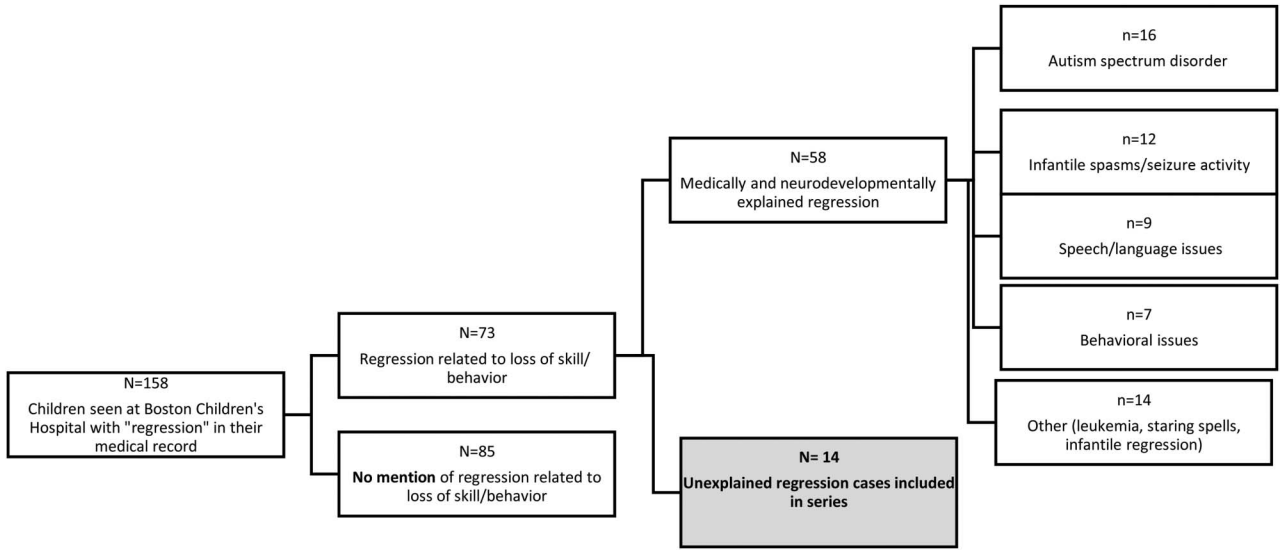

Figure 1. Flow chart of selection of the 14 unexplained regression cases, showing the selection process for inclusion in this case series at Boston Children's Hospital Down Syndrome Program. Initially, 158 patients with a diagnosis of DS and the presence of the phrase "regression" in their medical records were identified using medical record query. Those with no documented loss of skills (n = 85) were eliminated. Fifty-eight of the remaining patients had a documented medical cause for their regressive symptoms, such as autism spectrum disorder, infantile spasms, leukemia, infantile regression, and staring spells. Issues exclusively related to speech and language and disruptive behaviors were not included because they did not meet our definition for regression. Other explanations for regression such as treatment for leukemia and infantile regression were also excluded. The remaining 14 individuals were examined in detail in this case series. The oldest individual in the original query looking for regression (N = 158) was 24 years, an age before the onset of Alzheimer disease; therefore, it was not investigated.

to a chronic decline over several years. Onset of regression symptoms to presentation to the BCH DSP clinic ranged from three months to six years (mean = 2.2, SD = 1.9). All 14 individuals experienced a decline in abilities relating to procedural memory; most (n = 13) also experienced social withdrawal and a deterioration in their functional ADLs, speech, and social skills (see Table 2). Eight individuals had a family history of mental health and/or learning problems. Educational placement varied: seven attended substantially separate (i.e., self-contained) classrooms, five were in partial inclusion classrooms, and one was in a full inclusion classroom.

All 14 individuals in our case samples underwent varying degrees of diagnostic evaluation. Workup consisted of blood work (e.g., complete blood count, chemistry, and thyroid function tests) and in some cases also included neuroimaging (brain MRI), EEG, and sleep studies. The results from these studies were largely unremarkable. Patients also received varying modes of treatment that included behavioral and therapeutic supports, immunotherapy, psychopharmacologic therapy, and ECT. Treatment outcomes varied among individuals. Some individuals in the cohort regained some skills over the course of treatment, but only two returned to the baseline level of functioning. Of the two, one continues to need treatment with ECT, and both continue to need psychosocial supports.

All 14 individuals experienced at least one psychosocial stressor in the year before regression. Thirteen individuals experienced two or more stressors, at times overlapping with one another, with two individuals experiencing stressors in all four categories (see Table 3). The individual who experienced one psychosocial stressor (hospitalization/medical procedures) experienced multiple procedures and hospitalization. There was often an overlap in psychosocial stressors, with patients experiencing several types of stress, including (1) traumatic events (e.g., medical trauma from hospitalization, abuse, death of a family member, or a highly stressful event immediately preceding the decline in functioning), (2) adolescent transitions, (3) changes in home, (4) changes in school, and (5) changes in social relationships. The most common psychosocial stressor was changes in school.

The following nine cases illustrate the occurrence of psychosocial stressors and examples of each type of stressor present. The remainder of the case vignettes are available in the supplement (Supplemental Digital Content 1, http://links.lww.com/JDBP/A364) and show similar examples of psychosocial stressors demonstrated here. Patient initials were changed to preserve anonymity.

Traumatic Events: Abuse or Highly Stressful Event

Some individuals experienced abuse or a highly stressful event before regression. In some cases, regression occurred immediately after the traumatic event, and in other cases, the regression occurred many months later after additional exposure to stressors.

Case 1

ID was a 20-year-old woman who presented with a gradual decline in the year leading up to regression. Before regression, she spoke in fluent sentences, fed herself independently, and slept well. She participated in

Table 1. Sociodemographic, Medical History Characteristics, and Regression Trajectory of Unexplained Regression in Down Syndrome Cases

	Demographic Characteristics					Co-Occurring Medical Conditions					Co-Occurring Mental Health Conditions and Neurodevelopmental Disorders						Bush-Francis Catatonia Scale	
	Sex	Age	Onset	Race	Income Quartile	Congenital Heart Disease	Hypothyroidism	Sleep Problem	Overweight	Other	Catatonia	Depression	Anxiety	Adjustment Disorder	Autism Spectrum Disorder	Other	Baseline	PEAK
ID	F	20	1 yr	Other	Upper	YES	0	0	o	o	YES	YES	o	0	o	o	1	16
TB	M	17	4 yr	White	Middle	YES	0	0	o	YES	o	YES	YES	o	o	YES	—	—
LV	M	11	4 yr	African-American	Moderate	YES	0	YES	o	o	YES	o	o	o	o	o	2	22
BD	M	17	2 yr	White	Middle	o	0	YES	o	o	o	o	o	YES	YES	0	6	18
JD	F	14	1 yr	White	Middle	o	0	YES	o	o	YES	YES	o	o	o	o	—	22
JE	F	19	6 yr	White	Upper	o	YES	0	YES	o	YES		o	o	o	o	1	18
ZE	F	19	2 yr	White	Middle	YES	YES	YES	YES	o	o	o	o	o	o	YES	—	10
IN	F	13	3 mo	White	Moderate	o	0	0	o	YES	YES	YES	YES	YES	o	o	1	15
IX	M	12	2 yr	White	Moderate	YES	YES	0	o	o	o	o	o	YES	o	YES	3.5	32
LC*	F	13	2 yr	White	Middle	YES	0	YES	o	o	o	o	o	YES	YES	0	—	—
BL*	M	7	2 yr	White	Upper	YES	0	0	0	YES	o	o	o	o	o	o	—	7
IM*	M	20	1 yr	Other	Low	o	0	YES	YES	o	o	YES	o	o	o	YES	—	—
CT*	F	20	3 mo	White	Middle	o	0	0	o	o	o	YES	YES	YES	o	YES	1	5.5
ZD*	F	17	1 yr	White	Moderate	o	0	0	o	YES	YES	o	o	o	o	o	—	—

Patient initials were changed to preserve anonymity. Information was collected regarding demographic, medical, mental health, neurodevelopmental, and regression trajectory history for 14 cases seen from 2015 to January 2021 at the Boston Children's Hospital Down Syndrome Program. For the age of onset, yr, years; mo, months. Income quartiles were divided on median household income per patient's zip code: low (<$34,282/yr), moderate ($34,282≥ × <$54,850), middle ($54,850≥ × <$82,276), and upper (≥$82,276) (Johnson, et al, 2013). YES indicates the presence of a co-occurring medical, mental health, or neurodevelopmental disorder; 0 indicates its absence. For co-occurring medical conditions, sleep problems include obstructive sleep apnea and behavioral sleep disorder, whereas other medical conditions include acute pancreatitis, Sydenham chorea, precocious puberty, leukemia, and Hashimoto disease. For co-occurring mental health or neurodevelopmental disorders, other mental health conditions and neurodevelopmental disorders include behavioral disorder, mood disorder, and psychotic disorder/hallucinations. The Bush-Francis Catatonia Scale is a standardized tool designed to screen and diagnose catatonia. The scale is a 23-item rating scale, with items 1 to 14 used as a screening tool. Items 1 to 14 are marked as absent (0) or present (3). The presence of 2 or more of the screening items for 24 hr or longer would meet the diagnostic criteria for catatonia. For severity, items 1 to 23 are rated using a scale of 0 to 3, the score is the sum responses of all the items. The higher the score, the higher the severity (Bush et al., 1996). For specific patients, their baseline (preregression) and PEAK score (at the time of regression) were included in this table.
*Five individuals were included in analyses but not described in the current article but available in the supplemental material.

Table 2. 28-Feature Definition Proposed by the Regression Working Group of the Down Syndrome Medical Interest Group for Unexplained Regression in Down Syndrome Cases

Twenty-Eight Core Features of Unexplained Regression with an Onset of 3 months or Longer		ID	TB	LV	BD	JD	JE	ZE	IN	IX	LC*	BL*	IM*	CT*	ZD*
Core features	Adaptive functioning														
	Social skills: withdrawal, avoidance, isolation; time spent alone	YES	YES	YES	YES	YES	YES	YES	YES	YES	0	YES	YES	YES	YES
	Functional ADLs: loss of acquired skills; dependent (not just slower)	YES	YES	YES	YES	YES	YES	YES	YES	YES	0	YES	YES	YES	YES
	Speech: reduced, infrequent; whisper, monosyllabic, or mute	YES	YES	YES	YES	YES	YES	YES	YES	YES	0	YES	YES	YES	YES
	Cognitive-executive functioning														
	Attention: atypical, odd; gaze aversion, poor eye contact, or impaired ocular control	YES	0	YES	YES	YES	YES	YES	YES	YES	0	YES	0	YES	YES
	Functional skills: loss, confused, disorganized; unable to function school/job	YES	YES	YES	YES	YES	YES	YES	YES	YES	0	YES	YES	YES	YES
	Procedural memory: less able to perform or performs with assistance needed, regarding ADL routines or favorite activities	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	Learning memory: diminished working memory; not processing or learning	YES	YES	YES	YES	YES	YES	YES	YES	YES	0	0	YES	YES	YES
	Planning, organizing: not goal directed, disorganized	YES	0	YES	YES	YES	YES	YES	YES	0	0	0	YES	YES	YES
	Declarative memory: forgetful and confused regarding people, places, and events	YES	0	0	YES	0	YES	YES	YES	0	0	0	0	YES	YES
	Motor control														
	Initiation motivation: abulia, avolition, mutism	YES	0	YES	YES	YES	YES	YES	YES	0	0	YES	0	YES	YES
	Stereotyped movements: tics, stereotypies	YES	0	YES	0	YES	YES	YES	YES	YES	0	YES	0	0	YES
	Catatonia	YES	0	YES	YES	YES	YES	0	YES	0	0	0	0	YES	YES
	Extrapyramidal: bradykinesia, freezing, cogwheel rigidity, tremor	YES	0	0	YES	YES	0	0	0	0	0	0	0	0	0
Common features	Behavior														
	Internalizing: apathy, withdrawal, mood, stereotype, SIB	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	0	YES	YES	YES
	Externalizing: hyperactivity, irritable, disruptive, agitated	YES	YES	YES	YES	0	YES	YES	YES	0	YES	YES	YES	YES	YES
	Mental health														
	Mood, emotion, self-regulation: depression, compulsions, psychosis, PTSD, anxiety, panic, ASD/DSDD	0	0	YES	YES	0	YES	YES	YES	YES	YES	YES	0	YES	YES
	Sleep disturbance: insomnia, circadian shift	0	0	YES	0	YES	YES	0	0	0	YES	0	YES	YES	YES
	Transition/change	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	Appetite: anorexia, weight loss	0	YES	0	0	0	0	0	0	0	YES	0	0	YES	YES
	Incontinence: urine, feces	0	YES	YES	YES	0	YES	YES	0	0	YES	YES	YES	0	YES
	Trauma/loss/grief	YES	YES	YES	YES	0	0	0	0	YES	YES	0	0	YES	0
	Puberty	0	0	0	0	YES	0	YES	0	YES	YES	0	0	0	0
	Illness/hospitalization	0	YES	0	0	0	YES	0	0	0	0	0	0	0	0
	Sleep apnea, seizures: evidence on PSG, EEG	0	0	0	0	0	0	0	YES	0	0	0	YES	0	0
	Other inflammatory, autoimmune condition	0	0	0	0	0	0	0	0	0	0	YES	0	YES	0
	Systemic illness: pain, surgery	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Autonomic: syncope, pallor, sweating	0	0	0	0	0	0	0	0	0	0	YES	0	0	0
	Vision, hearing: acute loss or deterioration	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Total No. of features:	17	13	18	18	16	19	16	17	14	10	13	12	19	19

The 28-feature definition of unexplained regression proposed by the regression working group of the Down syndrome Medical Interest Group (Santoro et al. 2020) was used to screen the 14 unexplained regression in Down syndrome cases seen at the Boston Children's Hospital Down Syndrome Program. YES indicates the presence of a co-occurring medical, mental health, or neurodevelopmental disorder; 0 indicates its absence/insufficient documentation in clinical note. Transition/change, trauma/loss/grief, puberty, and illness/hospitalization were all included if they caused emotional distress in the past year of regression diagnosis. ADL, activities of daily living; ASD/DSDD, autism spectrum disorder/Down syndrome disintegrative disorder; EEG, electroencephalogram; PSG, polysomnogram; PTSD, post-traumatic stress disorder; SIB, self-injurious behavior. *Five individuals were included in analyses but not described in the current article but available in the supplemental material. Patient initials were changed to preserve anonymity.

ballet and basketball and had friends. ID experienced loss of a family member, moving to a new home, and a new family member moving into the home. At age 19 years, her teachers noticed a gradual onset of rocking movements and ID speaking in whispers. A month before her presentation, ID had an argument with her mother during a vacation that triggered an acute loss of speech for three days. Although she regained her

Table 3. Psychosocial Stressors Within One Year of Onset of the 14 Unexplained Regression in Down Syndrome Cases

	Traumatic Events		Adolescent Transitions	Changes in Home				Changes in School				Changes in Social Relationships	
	Abuse or Highly Stressful Event	Hospitalization	Pubertal Changes and Teasing/Bullying	Moved to New Home	Parents Divorced/Separated	Family Member Moved Out	Family Member Moved In	Transition to New School	Classroom Changes	New Teacher	Change in Services	Friendship	Relationship
ID	YES	o	O	o	O	YES	o	o	o	o	o	o	o
TB	o	YES	O	YES	O	o	o	YES	o	o	YES	o	o
LV	o	o	YES	o	O	o	o	YES	YES	o	o	YES	o
BD	YES	o	O	o	YES	YES	o	YES	o	o	o	o	o
JD	o	o	YES	o	O	o	o	YES	o	YES	YES	o	o
JE	o	o	O	o	O	o	o	YES	o	o	o	o	o
ZE	YES	o	YES	YES	o	o	YES	YES	o	o	o	o	o
IN	o	o	O	o	o	o	o	o	o	YES	YES	o	o
IX	YES	o	YES	o	o	YES	o	o	o	YES	o	YES	YES
LC*	o	o	YES	o	o	o	o	YES	YES	YES	o	o	o
BL*	o	YES	O	o	o	o	o	o	o	o	o	o	o
IM*	o	o	O	YES	YES	o	o	o	o	o	o	o	o
CT*	YES	o	O	o	o	YES	o	o	o	o	o	YES	YES
ZD*	o	o	O	o	o	o	o	o	YES	o	YES	o	o

Information was collected regarding traumatic events, adolescent transitions, and changes in the home, school/services, and social relationships within one year before the onset of regression and caused significant distress for 14 patients seen in the Boston Children's Hospital Down Syndrome Program. Highly stressful events include death of a family member, witness to violence, awareness of disability, parental conflict, and test failure. Adolescent transitions, such as pubertal body changes, changes in peer relationships, and teasing/bullying, were included if they caused distress. *Five individuals were included in analyses but not described in the current article but available in the supplemental material. Patient initials were changed to preserve anonymity.

speech, she spoke rarely and often in a whispered tone, and she giggled and laughed without apparent reason. Additional features included slow movements and losing the ability to feed herself. ID is receiving pharmacologic therapy with benzodiazepines for catatonia and selective serotonin reuptake inhibitors (SSRIs) for depression. She is talking more and has made progress in self-feeding, but she is not back to her baseline.

Traumatic Events: Medical Trauma (Either from Hospitalization or from Undergoing a Procedure)

There were individuals who experienced significant medical trauma, either from hospitalization or from undergoing a procedure. These events seemed to contribute or worsen an already ongoing regression.

Case 2

TB presented to the BCH DSP with regression at age 17 years. Before regression, he spoke in sentences, played on his iPad, listened to music, and dressed himself. At age 13 years, he transitioned to different schools and was eventually placed in several residential programs over the years. Over the next few years, he experienced symptoms of regression that included extremely challenging behaviors (e.g., disrobing and aggression) and diminished language. He was admitted for acute pancreatitis in June 2017 at age 16 years. After admission, TB became nonverbal, no longer dressed himself, and refused to eat when other people were present. He engaged in picking his skin. He received pharmacologic therapy with seizure medications for their mood-stabilizing effect as well as alpha agonists and benzodiazepine for mood and challenging behaviors. His regression has stopped with placement in a residential facility that seems to be a good fit. His mother describes his course as "ebbing and flowing" with placement, services received, and a peer group that is available to him significantly affecting his mood and behaviors.

Adolescent Transitions

The distress of adolescent transitions, including pubertal body changes and changes in peer relationships, emerged as a major theme for many of the individuals with DS. Five patients (36%) had their family explicitly state undergoing puberty as a stressor. Relatedly, because these individuals progressed through school and the gap between themselves and their peers widened in academics, adaptive, social, and play skills, they experienced distress because they had increasing awareness of their disability. Many experienced teasing or bullying, and these events preceded regression.

Case 3

LV is a 15-year-old adolescent boy whose regression symptoms appeared when he was 11 years old. Before regression, LV spoke in single words and phrases, followed 1-step instructions and some 2-step instructions, and loved to interact and play with his peers. At age 10 years, he became more aware of his difficulty adapting because of his developmental delays and encountered challenges when playing with peers. When he tried to play sports with same-age children, he often got pushed out of the way. When he tried to play with younger and developmentally appropriate peers, they were intimidated

by his large size, or he was excluded by their parents. At age 11 years, LV had gradual loss of language (spoke in single words and at times was nonverbal), lost ability to follow simple instructions, had sleep disturbances, developed incontinence, and had repetitive behaviors such as rocking back and forth and flicking paper. His mother has reported that LV started to have more stimming behaviors with the onset of puberty (indicated by adult hair patterns and increased penile size). LV was started on benzodiazepines for catatonia, an antiviral and dopamine agonist (amantadine). His regression has stopped, but he has yet to regain social skills and the language that he has lost.

Changes in Home

A major theme that emerged was individuals who experienced changes in their home in the year before regression. Losses could be due to a relative moving away or parental divorce with decreased time with one parent. In some cases, family members noted the psychosocial stressor as a trigger for the cascade of events that led up to regression or worsening an already occurring gradual regression.

Case 4

BD was a 17-year-old adolescent boy with autism spectrum disorder who presented at age 17 years, two years after the onset of regression. Before regression, BD made simple requests, fed himself, dressed himself with minimal assistance, and wrote and recognized his name. Reading was an area of strength, and he loved to read Disney books. At age 10 years, BD experienced physical and verbal abuse from an aide while at his prior school setting. Despite this, he seemed to be resilient. A year before regression, his parents divorced, and he transitioned to a new school. At age 15 years, BD had an acute two-week episode of altered mental status when he developed drooling, rigidity, and flattened affect. He was admitted to a hospital. Regression episodes reoccurred at six to eight-month intervals, each lasting approximately two weeks. In the months before his presentation at clinic, intervals had shortened, occurring weekly. Scripting and echolalia significantly increased, and BD was now whispering his words. Additional symptoms include rigidity of limbs, blank facial expression, further reduced social interaction, unusual posturing (holding limbs antigravity for prolonged periods), self-injurious behavior, and loss of ability to feed and dress himself. He sometimes seemed to be responding to internal stimuli by looking over his shoulders. BD received treatment with benzodiazepines and leucovorin. At age 20 years, his symptoms resolved, and he is now at his baseline.

Changes in School

Some individuals experienced distress, which preceded regression, after transition to a new school or new community environment. Middle school and postsecondary programs were particularly challenging.

Case 5

JD was a 14-year-old adolescent girl diagnosed with regression, with onset starting at age 13 years, after transition to middle school. In an elementary school, JD was on the student council, participated in Best Buddies, and was described as very social. She carried conversations and asked questions. She was independent, preparing simple meals and dressing herself. At age 13 years, she struggled with transition to middle school, in a new educational environment and with new programming. Over the next 10 months, she had diminished speech, engaged in self-talk, and stopped wanting to meet with friends. On presentation, JD spoke only a few words a week, needed prompting to brush her teeth, and required assistance to shower and dress. She retreated to her family's basement and needed prompting to eat and finish meals. She had episodes of jerky movements, was sometimes unresponsive, had untriggered laughter, and "got stuck" washing her hands. Treatment consisted of SSRIs and benzodiazepines for catatonia and, ultimately, ECT. At age 20 years, JD's catatonia symptoms have resolved; however, she continues to need maintenance treatment with ECT (every 8 wk) or she regresses.

Case 6

JE was a 19-year-old woman who presented with gradual regression starting at age 13 years. She was "the life of the party" and loved to dance. She spoke in sentences and was toilet trained. At age 13 years, she transitioned to a new school. She began to lose interest in things and started speaking in fewer words. Over the course of six years, she developed incontinence, withdrew from her friends, started bolting, and flapped her hands repetitively. There were periods when symptoms plateaued and then worsened. By the time she presented to the BCH DSP at age 19 years, JE hit her head hundreds of times a day, rarely talked, and lost the ability to take care of herself. JE received pharmacologic treatment that included benzodiazepines and SSRIs. She also received steroids. Self-injurious behaviors have stopped, and her mood is better. She continues to have repetitive behaviors. ECT was recommended but has not yet started.

Case 7

ZE was a 19-year-old woman with regression who experienced a number of psychosocial stressors starting at age 11 years and loss of skills starting at age 15 years. At age 11 years, her house caught fire and burned down while ZE was home, and the family subsequently lived for three months in a hotel. Three grandparents also died before and after the fire. Despite these events, ZE seemed to do well, continuing previous activities and responded appropriately with intact social relationships. She transitioned to high school, and at age 15 years, she began speaking less and, at times inappropriately, was aggressive toward others in school, and responded to internal stimuli (seemed to be seeing/hearing something that was not there). She withdrew socially and engaged in self-injurious behaviors. At age 17 years, her loss of skills progressed to incontinence, reduced academic skills, development of motor stereotypies ("playing the

piano" movements) and inappropriate laughter, perseveration of normal movements (turning pages of the book without reading), and psychomotor slowing. ZE received pharmacologic therapy with benzodiazepines for catatonia and SSRIs. ZE's aggressive episodes decreased, her eye contact improved, and she is using more words.

Case 8

IN was a 13-year-old adolescent girl who presented with a three-month history of regression. Before regression, she spoke in sentences, engaged in conversations, had robust nonverbal communication, and was very social. Six months before regression, her aide at school was changed from being someone who understood her well to someone who did not fully implement her educational accommodations. This coincided with the onset of the coronavirus disease 2019 (COVID-19) pandemic lockdown, resulting in drastic lifestyle changes. After the lockdown, she had an increase in abnormal movements, a decrease in functional speech, and an increase in dysfunctional speech (verbigeration/perseveration/echo). She spoke in a whispered tone. Treatment consisted of benzodiazepine, an SSRI, and atypical antipsychotics. She is more engaged but has not yet regained her baseline level of functioning.

Changes in Social Relationships

The following case illustrates the loss of peer group and social relationships after graduation. It also illustrates how individuals experienced an overlap of psychosocial stressors; in this case, trauma, changes in the home, and changes in school are also evident.

Case 9

IX was a 12-year-old boy who had been experiencing a gradual decline over 6 months when he presented. At baseline, he was "the mayor of the school," had back and forth conversations, played board games with appropriate turn-taking, was toilet trained, dressed himself, and read books. Psychosocial stressors in the past year included witnessing violence from a peer in school toward a beloved teacher who then left the school, grandparents and other family members moving away, a parent working away from home for three months, and the loss of a peer group after graduation. After these events, IX presented with social withdrawal, a decline in speech, decreased participation in hedonic activities, loss of adaptive skills (e.g., dressing and toileting), and an increase in repetitive behaviors including pacing and playing with tissue. IX was trialed on several medications, including benzodiazepine, none of which were helpful. He is currently receiving ECT and has regained purposeful activities but is far from baseline.

DISCUSSION

In this review of 14 cases of URDS, all individuals experienced at least one and often several psychosocial stressors in the year preceding regression. Many of the stressors were identified as triggers for regression by families. There was often an overlap in psychosocial stressors, with individuals experiencing stressful events. The most common events identified preceding regression were changes in school. Interestingly, many of the psychosocial factors identified with the onset of regression in this cohort of individuals with DS are relatively common life events (e.g., puberty, school transitions, and small family arguments), yet regression is not reported as often in response to these events in the general population. It is not known why these life events contribute to regression in some and not others. Stressors may affect each individual differently.

The relationship between psychological stress and mental illness has been described and has been influenced by the characterization of the stressor, biology of the individual, and quality of psychosocial supports.[17] The salience, amount, and persistence of the stressor(s) are important factors that affect the relationship between stress and impact on the individual.[17] An individual's resilience mechanisms, derived from genetics, environment, education, and familial factors, also play a role in moderating the impact of stress.[18]

Rosso et al[8] described a proposed pathophysiology wherein an external stressor is more prone to trigger regression when experienced by an individual who has a diminished capacity to cope with stress. In this pathway, immune dysregulation leads to neuroinflammation, whereby autoantibodies and cytokine dysregulation may play a role. Poumeaud et al[18] subsequently described DS itself as a risk factor for stress and poor resilience in that individuals with DS may perceive stressful events with the same intensity whether they are the more common events (e.g., change in or loss of caregiver) or harsh events (e.g., assault or abduction) and that these stressors overwhelm adaptive capacities. Individuals with DS may pass a critical recovery threshold more quickly and therefore not recover as well, or not recover at all, from stressful events. Events may subsequently lead to symptoms not unlike those of post-traumatic stress disorder (PTSD).[18]

Another explanation may be that significant life events trigger an acute stress response that starts a cascade of events in these individuals, which then manifests as regression. Learned patterns of coping, or the ways in which individuals respond to psychosocial stressors, greatly affect an individual's quality of life.[19] For instance, positive coping styles lessen the effect of stress or trauma, whereas negative coping styles may create more distress and/or mental illness.

Adolescence is marked by significant changes in body and behavior.[20] For individuals with DS and intellectual disability, it is a period of vulnerability because they navigate medical, educational, and social transitions.[21] In our cohort, five patients struggled with these changes, experiencing distress because they became increasingly aware of the social gap between them and their peers and because they went through puberty including bodily changes and the onset of monthly menstrual periods for girls. Stress related to pubertal and adolescent changes has also been demonstrated for individuals with other

genetic conditions such as Prader-Willi syndrome; these individuals can have incomplete sexual development and have a complex neurodevelopmental profile.[22,23]

It should be noted that extensive diagnostic evaluations in this sample did not reveal clinically significant findings, and treatment outcomes were suboptimal despite the use of multiple treatment modalities. These findings were similar to those in other studies.[3,9] Behavior therapy and psychosocial supports were in place for some individuals before regression and were often recommended as a component of the treatment plan. However, given the striking occurrence of psychosocial stressors in this study, it is possible that these strategies are underemphasized in URDS.

Indeed, psychosocial stressors are potentially overlooked in the midst of extensive diagnostic evaluation. Thus, treatment of mood problems and targeted interventions, such as considering current school placement or prioritizing social relationships during disruptions, may not be performed in a timely manner or at all. A better understanding of psychosocial stressors may help clinicians identify individuals at risk for URDS and begin to address appropriate interventions alongside the medical workup, which is often challenging to tolerate and low yield with regard to informing treatment plans. Preventive strategies and use of a well-documented stress response approach are known to be beneficial to individuals with DS.[24,25] Specifically, implementing a comprehensive transition plan for major changes to routine, addressing and intervening bullying concerns, and maintaining structure and meaningful social engagement, in addition to coping skill development and consideration for psychopharmacological treatment, may increase resiliency in individuals with DS.

Several limitations to this study should be noted. Owing to the retrospective nature of this study, not all the psychosocial stressor information was documented in a uniform way. Although some clinic notes may have gone into thorough detail about the various factors, many of the notes lacked sufficient details to understand the impact of each psychosocial stressor. In addition, because many of these cases were captured retrospectively, many of the regression features, onset history, and laboratory work were pulled from previous clinic notes and not collected in real time. Thus, much of the needed information is documented as missing. Owing to so much variability in treatment options across the cases, no conclusions could be made on what treatments were most effective, and it was decided that this would not be a focal point of this article. Future research is needed to include and analyze the treatment modalities. In this case series, one individual had psychosocial stressors that were exacerbated by the COVID-19 pandemic. Future work exploring the impact of COVID-19 on mental health in DS, and its role on URDS, is also needed. All cases were from one tertiary care center.

Future research is needed to understand the mechanism and biology of URDS. Future research will focus on examining the relationship between psychosocial factors and stressors, regression, and developmental outcomes in URDS using a prospective and streamlined approach with comparison groups.

CONCLUSION

This study, involving a retrospective chart review of 14 cases of URDS, highlights that psychosocial stressors are commonly reported preceding URDS. A better understanding of the triggers and etiology of URDS, and the role of psychosocial stressors in this process, can help inform prevention, diagnostic, and treatment strategies. Increased emphasis on psychosocial support strategies, such as services and individual and family therapy and resources, may improve outcomes in URDS. Future research will use a prospective approach, with a matched control group of individuals with DS, to explore the relationship between psychosocial factors and URDS, and the impact of this relationship on future outcomes for individuals with DS.

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