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ORIGINAL ARTICLE

Unexplained regression in Down syndrome: Management of 51 patients in an international patient database

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Abstract

Research to guide clinicians in the management of the devastating regression which can affect adolescents and young adults with Down syndrome is limited. A multi-site, international, longitudinal cohort of individuals with a clinical diagnosis of Unexplained Regression in Down syndrome (URDS) was collated through seven Down syndrome clinics. Tiered medical evaluation, a 28-item core symptom list, and interim management are described naturalistically. Improvement—defined by the percentage of baseline function on a Parent-reported Functional Score, overall improvement in symptoms on a Clinician-administered Functional Assessment, or report of management type being associated with improvement—was analyzed. Improvement rates using ECT, IVIG, and others were compared. Across seven clinics, 51 patients with URDS had regression at age 17.6 years, on average, and showed an average 14.1 out of 28 symptoms. Longitudinal improvement in function was achieved in many patients and the medical management, types of treatment, and their impact on function are described. Management with intravenous immunoglobulin (IVIG) was significantly associated with higher rate of improvement in symptoms at the next visit ($p = 0.001$). Our longitudinal data demonstrates that URDS is treatable, with various forms of clinical management and has a variable course. The data suggests that IVIG may be an effective treatment in some individuals. Our description of the management approaches used in this cohort lays the groundwork for future research, such as development of standardized objective outcome measure and creation of a clinical practice guideline for URDS.

KEYWORDS

catatonia, Down syndrome, Down syndrome disintegrative disorder, regression, trisomy 21, unexplained regression in down syndrome

Abbreviations: DSDD, Down syndrome disintegrative disorder; DS, Down syndrome; ECT, Electroconvulsive therapy; GEE, Generalized estimating equations; IVIG, intravenous immunoglobulin; TMS, Transcranial magnetic stimulation; URDS, Unexplained Regression in DS.

1 | INTRODUCTION

An unusual, uncommon regression in some patients with Down syndrome (DS), characterized by average age of onset in adolescence and key features occurring over a range of months to years: loss of skills, mood changes, and repetitive thoughts or behaviors, has gained awareness and interest (Akahoshi et al., 2012; Cardinale et al., 2018; Devenny & Matthews, 2011; Ghaziuddin et al., 2015; Jacobs et al., 2016; Jap & Ghaziuddin, 2011; Mircher et al., 2017; Prasher, 2002; Rosso et al., 2020; Tamasaki et al., 2016; Worley et al., 2015). Co-occurring psychosis, behavioral disturbances, and catatonia presenting with changes in motor activity, unusual movements, changes in speech, and changes in oral intake are described (Ghaziuddin et al., 2015). Our previous case–control data validated the core features of regression in adaptive function (change in functional Activities of Daily Living [ADLs], speech, and social skills), cognitive-executive function (functional skills, declarative memory, procedural memory, learning memory, planning/organizing, and attention), and motor control (stereotyped movements, extrapyramidal, initiation-motivation, and catatonia); common features of behavior and mental health (Santoro et al., 2020). Several diagnostic labels are used to describe this entity, including: Down syndrome disintegrative disorder (DSDD; Cardinale et al., 2018; Worley et al., 2015) catatonia, (Ghaziuddin et al., 2015; Jap & Ghaziuddin, 2011) acute regression, (Mircher et al., 2017) and Unexplained Regression in DS (URDS; Santoro et al., 2020) The term Unexplained Regression in Down syndrome (URDS) is used to describe this entity in this manuscript.

Ideally, identifying the etiology of URDS would guide treatment. Although possible causes have been suggested (early Alzheimer's disease, disruption at transition to adulthood or in self-identity, and autoimmunity Cardinale et al., 2018; Ghaziuddin et al., 2015; Prasher, 2002) and medical contributors can exist (Akahoshi et al., 2012; Jacobs et al., 2016; Mircher et al., 2017; Worley et al., 2015) with triggering stressors or adverse circumstances possibly playing a role (Santoro et al., 2020), bthe etiology for URDS remains unclear. Without a clearly-established etiology, case series have focused on management approaches to treat the clinical symptoms of URDS. Published studies have found variable improvement in URDS with the use of low-dose psychotropic medications (antipsychotics, SSRIs, and anticholinergic drugs for treating neuropsychiatric disturbances and high-dose benzodiazepines for treating features of catatonia), electroconvulsive therapy (ECT; Ghaziuddin et al., 2015; Jap & Ghaziuddin, 2011), and/or immunotherapy (intravenous/oral steroids, mycophenolate mofetil, intravenous immunoglobulins, rituximab; Cardinale et al., 2018; Hart et al., 2021; Rosso et al., 2020). Transcranial magnetic stimulation (TMS) is another treatment for neuropsychiatric disorders including catatonia: however, while TMS is noninvasive and increasingly available, it is less investigated for use in individuals with URDS to date (Camprodon et al., 2016; Rosso et al., 2020; Slotema et al., 2010; Sun et al., 2016).

In choosing a treatment course, multiple factors should be considered. The cost, insurance coverage, side effects, availability, and legal implications for people with intellectual disability play a role into treatment choice. Further, specialists experienced in the use of ECT or immunotherapy may be geographically-limited. The risk of longer-term side-effects, the necessity for long-term treatment and long-term response to treatment are also considerations. However, the long-term course and treatment response of URDS is not well-described in the literature, with only 11 longitudinal cases followed for 6–31 months (Cardinale et al., 2018; Ghaziuddin et al., 2015; Jap & Ghaziuddin, 2011; Tamasaki et al., 2016) and each studying a specific treatment. Among these, four patients treated with a benzodiazepine and ECT recovered to baseline function prior to onset of catatonia symptoms (Ghaziuddin et al., 2015), and seven patients treated for 2.7–6 years recovered to 90%–100% of their baseline function with the use of benzodiazepine (oral and/or IV lorazepam) or ECT (Ghaziuddin et al., 2015; Miles et al., 2019).

Geneticists may seek more information on the long-term course and treatment response of URDS to guide physicians and families. To fill this literature gap, after previously describing the diagnostic features of URDS (Down Syndrome Medical Interest Group - USA - Home, 2019), we initiated this naturalistic study to describe the clinical course and management of patients with URDS. We compiled URDS data from patients with URDS in our multi-institutional, international DS database to answer the clinical questions: (1) How does function change over time? (2) How often does URDS resolve? (3) What types of management are received? (4) Are there features to differentiate those who will show clinical improvement? (5) Are there any diagnostic variables, such as presence of catatonia, that are associated with specific management types that lead to improvement? We aimed to track improvement with ECT, IVIG, and other treatments. Since the entity of URDS is still new and emerging, we hoped to describe an ecological study of the effects of treatment in real-world clinics, in real-time. As geneticists are a trusted source of medical information for patients with Down syndrome, awareness of the longitudinal course and management of URDS can directly impact patient care, inform collaboration with other medical subspecialists and primary care physicians, and guide discussion with families of patients with URDS. We hope this manuscript might be a reference for clinicians who are looking into the approaches for regression, with references to guide them to more robust studies of each treatment type. We further hope that the lessons learned from this study can guide future researchers and serve as preliminary results for more rigorous clinical trials in the future.

2 | METHODS

2.1 | Population

An experienced, international DS clinic consortium, the International Down Syndrome Patient Database, with a track record of clinical research and publication served as a pipeline for collecting clinical cases of URDS (Lavigne et al., 2015; Lavigne et al., 2017; Sharr et al., 2016). The Institutional Review Boards at Massachusetts General Hospital, University of Pittsburgh, The University of Queensland,

Mater Misericordiate Ltd, Duke University Medical Center, Boston Children's Hospital, Geisinger, and Bambino Gesu Children's Hospital approved this study. Database consent was obtained during or following a visit to each site's specialty clinic, or a waiver of consent was obtained for retrospective chart review. Each site collected and maintained data in REDCap® (Harris et al., 2009). Inclusion criteria were: (1) a clinical diagnosis of URDS, using the clinical judgment of experienced physicians in subspecialty clinics for DS previously shown to be able to clearly distinguish between patients with DS and regression, and patients with DS without regression, (2) consent to participate in the international database, (3) a clinic visit to a participating site. Exclusion criteria: Not meeting inclusion criteria. All information is presented in de-identified aggregate form. The de-identified, aggregate data that support the findings of this study are available on request from the corresponding author. The data are not publicly available as data sharing outside the consortium was not discussed in the consent process.

2.2 | Data collection: Clinician-rated data

As outlined in our previous study (Santoro et al., 2020), consortium sites reviewed patients with URDS on monthly conference calls, and collected a standard set of data through retrospective chart review using a common data dictionary of fields and responses in REDCap (Santoro et al., 2020). The standard set of data collected for each subject included clinical details from (1) a 28-item definition of regression proposed by the chair of the regression working group of the Down Syndrome Medical Interest Group including core and common features - the 28-item URDS symptom list (Santoro, 2020), and (2) a tiered medical evaluation (Jacobs et al., 2016). As outlined previously, the first tier of our medical evaluation included bloodwork, imaging studies, hearing and vision screens, a polysomnogram, a screen for stressors and depression focused on the 6 months prior to the onset of decline using a published, unvalidated DS depression screen (Devenny & Matthews, 2011; Santoro et al., 2020). Laboratory values were recorded based on each institution's normal range. All studies were not collected at all sites; patients who did not have a given evaluation completed were not included for that single parameter.

Additionally, in this study, a new management dataset included (i) management received prior to diagnosis visit, (ii) interim management at subsequent visits, (iii) interim clinical status, and (iv) details of treatment, completed by the clinician at follow-up visits. Questions included: "Since last visit, has your patient received any of the following to address regression?" with response options of "Management or treatment of co-morbidities", "Behavioral management", "Pharmacologic management", "ECT", "TMS", "IVIG", and "Other". Then, "Did X management coincide with any improvement in regression symptoms?" with response options of "Yes", "No", and "Ongoing". For those treatment modalities which coincided with improvement in symptoms, the specific details of the treatment regimen were asked.

2.3 | Clinician-administered and parent-reported measures

For the purpose of this project, we created two measures, the Parent-reported Functional Score and the Clinician-administered Functional Assessment. The Parent-reported Functional Score assesses general function with scores reported from 0% to 100% in which 100% means completely back to premorbid baseline prior to onset of URDS. Specifically, to obtain the Parent-reported Functional Score, clinicians asked parents "Overall, in the judgment of the parents, how does function compare to baseline prior to regression (in % of baseline function)?". The Clinician-administered Functional Assessment evaluates global function from the last visit to present; clinicians answered the question "Overall, how does function compare to previous visit?" with five response options of: "completely resolved", "improved, with significant changes (waxing/waning) over time", "with minor changes (waxing/waning) in function over time", "with function generally stable over time", or "worsened" with input from caregivers during the clinical interview. These two assessments of function are novel and unvalidated.

2.4 | Data analysis

Standardized de-identified datasets from each center were compiled; data were summarized using means, standard deviations, percentages. Additionally, among those with data available, we analyzed two subgroups:

(1) Improvement: Symptoms at each follow-up visit were classified as improved versus not improved from the previous visit, with responses to the Clinician-administered functional assessment of "completely resolved" or "improved" treated as improvement and other responses as non-improvement using the Clinician-administered Functional Assessment. We conducted this analysis to identify any factors associated with improvement at a subsequent visit, and thus, focused on whether patients had improvement or not. Improvement was relative to function at previous visit and did not correlate to a specific Parent-reported Functional Score. Univariate analyses of the association between characteristics/types of management and improvement in symptoms from the previous visit were performed. Generalized estimating equations (GEE) models were used because GEE models account for repeated assessment of symptoms within each patient. No patients were treated with TMS, so this was not analyzed.

(2) Presence of catatonia: Patients were grouped into two cohorts: those with Clinician-administered catatonia present at diagnosis visits, and those without. The presence of catatonia was based on the clinical feature of "catatonia, with an onset of three months or greater" as one of the core features of motor control symptoms. Among patients with catatonia present, we examined the association between characteristics/types of management and improvement using GEE models. Instability was seen in some of the models with few visits; treatments with ≥10 visits were included.

Data Availability: The data are not publicly available as data sharing outside the consortium was not discussed in the consent process.

3 | RESULTS

We present our results data at both (1) the patient-level to describe the overall cohort and inter-patient differences, and (2) the visit-level to describe an individual's overall course and management impact.

From April 2017 to June 2020, we identified 51 patients with URDS, of whom, 21 were previously-reported (Santoro et al., 2020) and 30 were new patients (Figure 1; Santoro et al., 2020) Demographic details showed average onset of regression at 17.6 years, slight male predominance, and primarily white race (Table 1). Four patients had relevant family history including autism in twin brother, Graves' disease in mother, bipolar disorder in sibling, and depression, anxiety, and substance abuse. Patients had a mean score of 14.1 symptoms (range: 1–22) on the 28-item URDS symptom list at first visit, had experienced an average of 0.9 stressors, and an average of 4.6 depressive symptoms in the 6 months prior to the onset of regression symptoms (Table 1). All 51 patients had diagnosis data available which could include Parent-reported Functional Score at diagnosis (Table 2), and management prior to first visit; 45 patients had follow-up visits with interim management (Table 3).

3.1 | Longitudinal - (1) how does function change over time?

To follow function and symptom resolution over time, patients were followed over 3 clinic visits on average (range = 1 to 12 visits) using the Parent-reported Functional Score. Average function at diagnosis was 57.1% (*SD* = 14.5) on Parent-reported Functional Score for 12 visits. Average function at the lowest point in the course of regression was 22.2% (*SD* = 6.3) for 9 visits, indicating that the lowest function was often prior to diagnosis (Table 2). In some instances, the date at lowest function was known, but not the percent function. The median time at lowest point in the course of regression was 11 days prior to clinic diagnosis visit (mean = 592 days prior, range = 0–5772 days; *SD* = 1558). The mean Parent-reported Functional Score at the most recent follow-up visit was 75.4% (*SD* = 23.7) for 24 visits; this occurred on a median of 680 days after diagnosis (mean = 1000 days, *SD* = 980; range = 0–4004 days). Among the 15 patients with Parent-reported Functional Score reported at more than one visit, we found that change was +26% of baseline function from the first visit when function was reported to the most recent visit when function was reported on Parent-reported Functional Score (Table S1, Figure S1). Six patients had longitudinal scores on the 28-item symptom checklist (Figure S2).

3.2 | (2) How often does URDS resolve?

Visit-level function over time, on the Clinician-administered Functional Assessment, improved at 68 (47%) visits, worsened at 16 (11%), completely resolved at 12 (8%) visits, with function generally stable over time in 31 (21%) visits, with minor changes (waxing/waning) function over time in 19 (13%), and worsened in 16 (11%) visits (Table 2).

These visits correspond to 10 unique patients in our cohort who reached complete resolution in URDS symptoms (Table S2).

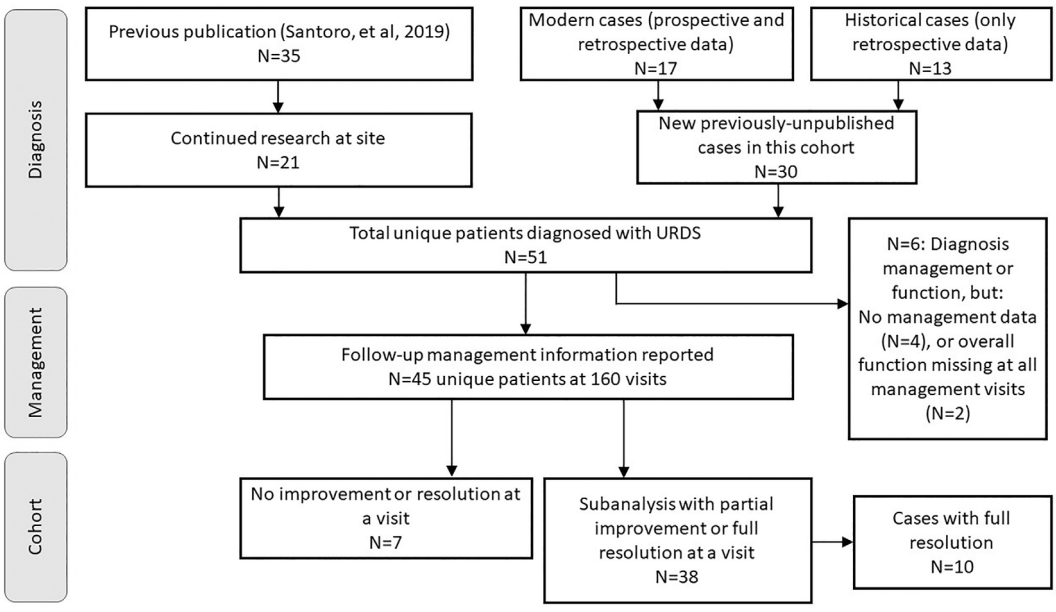

FIGURE 1 Flow chart of the 51 patients with unexplained regression in Down syndrome (URDS) included, of which 45 have management information reported at more than one visit

TABLE 1 Demographics of patients with unexplained regression in Down syndrome (URDS)

		Subgroups	
	Total cohort ($N = 51$)	Catatonia present cohort ($N = 27$)	Improvement cohort ($N = 38$)
	N (%)	*N* (%)	*N* (%)
Male	32 (63)	16 (59)	23 (61)
Race (choose all that apply)			
White	41 (80)	20 (80)	28 (74)
Black or African American	6 (12)	4 (15)	6 (16)
Asian	1 (2)	1 (4)	0 (0)
Other	1 (2)	0 (0)	0 (0)
Missing	3 (6)	2 (7)	2 (5)
Ethnicity			
Not Hispanic	43 (84)	24 (89)	31 (82)
Hispanic	2 (4)	0 (0)	2 (5)
Missing or Unknown	6 (12)	1 (4)	5 (13)
Site			
Bambino Gesu/Italy	6 (12)	0 (0)	1 (3)
BCH/Boston, MA	13 (25)	5 (19)	9 (24)
CHP/Pittsburgh, PA	7 (14)	5 (19)	7 (18)
Duke/NC	7 (14)	2 (7)	7 (18)
Geisinger/PA	1 (2)	1 (4)	1 (3)
MGH/Boston, MA	11 (22)	8 (30)	8 (21)
Queensland/Australia	6 (12)	6 (22)	5 (13)
		Mean ± *SD* (range)	
Age at regression	17.6 ± 6.2 (6–39)	19.6 ± 5.7 (12–39)	18.3 ± 6.1 (6–39)
Baseline IQ	42.1 ± 14.0 (9–70)	34.0 ± 14.7 (9–47)	46.0 ± 12.0 (40–70)
Number of visits	3.0 ± 2.7 (1–12)	2.0 ± 2.4 (1–10)	3.0 ± 2.9 (1–12)

3.3 | Management - (3) what types of management are received?

The types of management that were received varied. Before presenting to our clinics and/or being formally diagnosed with URDS, 25% of patients received pharmacologic management though medications were most often discontinued due to side effects or lack of efficacy, 12% had medical co-morbidities managed, and 6% received behavioral management (Table 3). Prior to the initial clinic visit, one patient received IVIG, and none had received ECT or TMS. The most common medical comorbidities treated were sleep apnea and hypothyroidism; only one patient had a medical co-morbidity identified which partially accounted for improvement in function, but symptoms were not fully accounted for by that medical diagnosis per clinician report. Three patients had a remaining untreated known medical condition (Table 3).

Pharmacologic management was used at 124 follow-up visits corresponding to 40 unique patients (Figure 2; Table S3), with improvement at 36% visits. Among those patients who showed improvement with pharmacologic management, the specific pharmacologic regimens varied, and polypharmacy was common (Table S2). Lorazepam was newly prescribed at 51 follow-up visits to 19 unique patients, and was included in their management regimen at the time of improvement at 30 visits corresponding to 14 unique patients.

At follow-up visits, medical co-morbidities were addressed at 12 of the 163 visits; sleep apnea remained prevalent and was the most common co-morbidity identified which accounted for a partial improvement. However, among those patients who had a medical co-morbidity which accounted for symptoms, symptoms were not fully accounted for by that medical diagnosis; there were persistent features of regression that remained unexplained, consistent with URDS.

At 163 follow-up visits, management included: behavioral management at 15%, ECT at 7%, IVIG at 15% (Figure 2, Table S3). Patients could receive more than one type of management at a given visit, and at different visits over time. At 49 visits, patients had received more than one types of management, and these included: pharmacologic + medical co-morbidities at five visits, pharmacologic + behavior at 13, pharmacologic + ECT at 6, pharmacologic + IVIG at 14, pharmacologic + other at 1, and pharmacologic + 2 other types of management at 10. When asked if management coincided with improvement in regression symptoms, improvement was associated with: pharmacologic management in

TABLE 2 Features and function from 51 cases with unexplained regression in Down syndrome

Clinician-reported 28-item checklist features present at first visit	*N*	(%)
Adaptive function (with an onset of 3 months or greater)		
Social skills: Withdrawal, avoidance, isolation; time spent alone	44	86
Functional ADLs: loss of acquired skills; dependent	45	88
Speech: Reduced, infrequent; whisper, monosyllabic or mute	45	88
Cognitive-executive function (with an onset of 3 months or greater)		
Attention: Atypical, odd; gaze aversion, poor eye contact, or impaired ocular control	39	76
Functional skills: Loss, confused, disorganized; unable to function at school/job	42	82
Procedural memory: Less able to perform or performs with assistance needed, with regards to ADL routines or favorite activities	44	86
Learning memory: Diminished working memory; not processing or learning	37	73
Planning, organizing: Not goal directed, disorganized	35	69
Declarative memory: Forgetful and confused with regards to people, places and events	22	43
Motor control (with an onset of 3 months or greater)		
Initiation-Motivation: Abulia, avolition, mutism	37	73
Stereotyped movements: Tics, stereotypies	31	61
Catatonia	27	53
Extrapyramidal: Bradykinesia, freezing, cogwheel rigidity, tremor	20	39
Behavior (with an onset of 3 months or greater)		
Internalizing: Apathy, withdrawal, mood, stereotype, SIB	44	86
Externalizing: Hyperactivity, irritable, disruptive, agitated	28	55
Mental health		
Mood, Emotion, Self-Regulation: Depression, Compulsions, Psychosis, PTSD, Anxiety, Panic, ASD/DSDD	36	71
Sleep disturbance: Insomnia, circadian shift	34	67
Transition/Change causing emotional distress in past 1 year	20	39
Appetite: Anorexia, weight loss	18	35
Incontinence: Urine, feces	21	41
Trauma/loss/grief, causing emotional distress in past 1 year	12	24
Puberty, causing emotional distress in past 1 year	11	22
Illness/Hospitalization, causing emotional distress in past 1 year	7	14
Sleep apnea, seizures: evidence on PSG, EEG	8	16
Other inflammatory, Autoimmune condition	6	12
Systemic illness: Pain, surgery	4	8
Autonomic: Syncope, pallor, sweating	4	8
Vision, Hearing: Acute loss or deterioration	0	0
	Mean ± *SD*	Range
Total score on 28-item URDS symptom list	14.1 ± 4.3	(1–22)
Number of depression symptoms on 39-item Depression screen (scale: 0–39)	4.6 ± 4.0	(0–15)
Number of stressors on 8-item Stressor screen (scale 0–8)	0.9 ± 1.1	(0–5)
Parent-reported Functional Score	Responses at a visit, *N*	% of baseline function, Mean (*SD*)
At diagnosis		
Overall, in the judgment of the parents, how does CURRENT function compare to baseline prior to regression?	12	57.1 (14.5)
Overall, in the judgment of the parents, how does function AT THE LOWEST POINT (the patient's 'worst' time) compare to baseline prior to regression?[a]	9	22.2 (6.3)
At first clinic visit		
Overall, in the judgment of the parents, how does function compare to baseline prior to regression?	11	47.6 (16.9)

TABLE 2 (Continued)

Clinician-reported 28-item checklist features present at first visit	*N*	(%)
At follow-up visit		
Any follow-up visit: Overall, in the judgment of the parents, how does function compare to baseline prior to regression?	69	66.0 (25.4)
Of those, at the most recent visit with response to: Overall, in the judgment of the parents, how does function compare to baseline prior to regression?	24	75.4 (23.7)
Clinician-administered Functional Assessment	*N* (%)	
At follow-up visit		
Overall, how does function compare to previous visit?		
Completely resolved	12 (8)	
Improved	68 (47)	
With function generally stable over time	31 (21)	
With minor changes (waxing/waning) in function over time	19 (13)	
Worsened	16 (11)	

[a]The date at lowest function was prior to diagnosis visit in 8 cases, and on the same date of diagnosis in 1.

36% of 124 visits, behavioral management in 8% of 24 visits, ECT in 73% of 11 visits, IVIG in 92% of 25 visits, and other management in 25% of eight visits (Table S3).

At the patient-level, all six patients who had ECT improved on, at least, one visit. Five of the six patients who received IVIG improved on, at least, one visit. Among the 12 patients who received ECT or IVIG, seven had catatonia (of whom, 5 received ECT, 2 received IVIG), and of these, all seven showed improvement; four of the five without catatonia who received ECT or IVIG showed improvement. Among those patients who showed improvement with other types of management, the IVIG dosing and ECT schedule varied among patients and, for some patients, changed over time (Table S2). Among the 10 patients who had complete resolution of regression symptoms, nine had catatonia, eight had resolution with pharmacologic and/or behavioral therapies, and one received IVIG.

3.4 | Improvement sub-analysis - (4) are there features to differentiate those who will show clinical improvement?

Forty-five patients with longitudinal management and function data were included in the improvement sub-analysis; 38 had at least one visit with improvement in symptoms (Table 4). Improvement or resolution was defined as a binary outcome at each visit; courses fluctuated. Improvement was relative to the previous visit in terms of Parent-reported Functional Score and could be relatively low at time of improvement; for example, at a visit when overall function had improved for one patient, the average Parent-reported Functional Score was 30%. Non-White patients were 1.32 times as likely to improve compared to their white peers (Rate of improvement 0.6760 in non-White race vs 0.5151 in White race, $p = 0.03$). Those with IVIG treatment were 1.64 times as likely to improve compared to those without IVIG (Rate of improvement 0.8206 in IVIG treatment vs 0.5016 in no IVIG treatment, $p = 0{\cdot}001$). To investigate further, a multivariable model with both race and IVIG management as covariates was performed. While the association between IVIG management and improvement remained significant (rate ratio [RR] = 1.53, $p = 0{\cdot}02$), the association with race was no longer significant (RR = 1.12, $p = 0.48$) suggesting there was not a true association between race and improvement and that the significance of the univariate association was due to confounding by IVIG management.

3.5 | Catatonia sub-analysis: (5) are there any diagnostic variables, such as presence of catatonia, that are associated with specific management types that lead to improvement?

Twenty-seven patients with URDS had catatonia present at diagnosis; those with catatonia were significantly older at regression diagnosis (median 19 vs 16 years without catatonia, $p = 0.0347$) and had higher URDS score at baseline (median 16 vs 13 without catatonia, $p = 0.0003$; Table S4). There were no differences in the number of stressors or number of depression symptoms between the cohort with regression and catatonia present and the cohort with regression and no catatonia. Univariate analyses of the association between management type and improvement within the catatonia subgroup were performed and indicated that specific management type was not predictive of improvement at subsequent visits within the catatonia cohort ($p > 0.05$, Table 4).

In summary, we found:

- Function partially improved with time and medical care: Average parent-reported function using the Parent-reported Functional Score was 22% of premorbid baseline function at the lowest point,

TABLE 3 Medical, behavioral, and pharmacologic management for participants with unexplained regression in Down syndrome ($N = 51$)

		Visits, *N* (%)	Unique patients, *N*
(A) Management or treatment of co-occurring medical conditions:			
(1) Prior to first visit, medical management to address regression, which:		6 (12)	6
Sleep apnea		4 (8)	4
Hypothyroidism		6 (12)	6
Hearing loss		1 (2)	1
Vision disease		1 (2)	1
Other		2 (4)	2
Missing		13 (25)	13
Have any medical co-morbidities been identified which account for change in function ($N = 30$ responses)?	Yes:	1 (3)	1
Sydenham chorea[a]		1 (3)	1
Are there any remaining untreated known medical conditions ($N = 31$ responses)?	Yes:	3 (10)	3
Headaches		1 (3)	1
Attention deficit disorder		1 (3)	1
Weight		1 (3)	1
(2) Since last visit, medical management to address regression, which:		12 (7)	8
Sleep apnea		5 (3)	3
Hypothyroidism		0 (0)	0
Hearing loss		0 (0)	0
Vision disease		0 (0)	0
Other: constipation		1 (<1)	1
At these ($N = 12$) visits, have any medical co-morbidities been identified which account for change in function?	Yes:	6 (50)	4
Obstructive sleep apnea (OSA)		4 (83)	2
Co-occurring OSA and constipation		1 (17)	1
Missing		1 (17)	1
Are there any remaining untreated known medical conditions?	Yes:	3 (2)	2
Headaches		1 (<1)	1
Sleep apnea/Co-occurring OSA and obesity		2 (1)	1
(B) Behavioral management:			
(1) Prior to first visit, behavioral management to address regression, which:		4 (8)	4
Cognitive Behavioral Therapy (CBT)		0 (0)	0
Applied behavior analysis (ABA)		1 (2)	1
General outpatient therapy		3 (6)	3
Of those ($N = 4$), did behavioral management coincide with any improvement in regression symptoms?[b]	Yes:	1 (25)	1
	Ongoing:	2 (50)	2
(2) Since last visit, behavioral management to address regression, which:		24 (15)	11
CBT		1 (<1)	1
ABA		2 (1)	1
General outpatient therapy		6 (4)	5
Type not specified, missing		15 (9)	4

TABLE 3 (Continued)

		Visits, *N* (%)		Unique patients, *N*	
(C) Pharmacologic management:					
(1) Prior to first visit, pharmacologic management to address regression:		13 (25)		13	
Was lorazepam used in the past?	Yes:	0 (0)		0	
Was >1 medication tried in the past?	Yes:	5 (10)		5	
Who was the primary person responsible for management?					
A psychiatrist		8 (16)		8	
A psychologist		1 (2)		1	
A neurologist		1 (2)		1	
Other		3 (6)		3	
If a medication was used in the past, why was it discontinued?		R × 1	R × 2	R × 3	R × 4
Side effect of medication		6	3	1	0
Challenges of treatment		0	0	0	0
Barriers to obtaining treatment		0	0	0	0
Medication efficacy		1	3	2	1
Attitudes or preferences of family		1	0	0	0
Other		0	0	0	0
		Visits, *N* (%)		Unique patients, *N*	
(2) Since last visit, was pharmacologic management used:		124 (76)		40	
Was lorazepam currently being used?	Yes:	51 (31)		19	
Was >1 medication currently being used?	Yes:	52 (32)		20	
Who was the primary person responsible for management?					
A psychiatrist		64 (39)		23	
A psychologist		3 (2)		3	
A neurologist		11 (7)		6	
Other		18 (11)		8	

[a]This medical co-morbidity did not fully explain URDS symptoms.
[b]Patients receiving a treatment could initially improve, then not show continued improvement.

48%–57% at initial clinic evaluation, improved to 66% at follow-up, and reached 75% at the most recent visit.

- A variety of management approaches were used: Management included treatment of medical co-morbidities, pharmacologic management, behavioral management, ECT, IVIG, and others, with some patients receiving management in multiple modalities simultaneously.
- IVIG or ECT were associated most frequently with overall improvement: Improvement occurred frequently in visits that were managed with IVIG (23 of 25, 92%) or ECT (8 of 11, 73%), often in visits that were managed with pharmacology (45 of 124, 36%), and rarely in visits that were managed with behavioral management (2 of 24, 8%).
- Statistical analysis of the association between characteristics/types of management and improvement in symptoms from the previous visit found that IVIG management ($p = 0.001$) was the only treatment type significantly associated with higher rate of improvement in symptoms.

4 | DISCUSSION

Regression in individuals with Down syndrome (URDS) has grown in its significance and representation in the literature (Ghaziuddin et al., 2015; Jacobs et al., 2016; Mircher et al., 2017; Rollin, 1946; Rosso et al., 2020; Worley et al., 2015). Building on our previous case–control study establishing the diagnostic criteria for this condition (Santoro et al., 2020), in this study, we describe the management of 51 patients with URDS and longitudinal data of the clinical course of 45 patients with URDS and visits to our seven international sites. Among the 10 patients with full resolution of symptoms, 8 resolved without IVIG, and were treated with pharmacologic and behavioral management.

Our results expand the existing literature, and our reporting of the longitudinal course and response to treatment of the largest cohort to-date may inform clinicians seeking guidance in care of URDS. This cohort had an average of 14 features on the 28-item symptom checklist, which aligns with the clinical diagnostic features

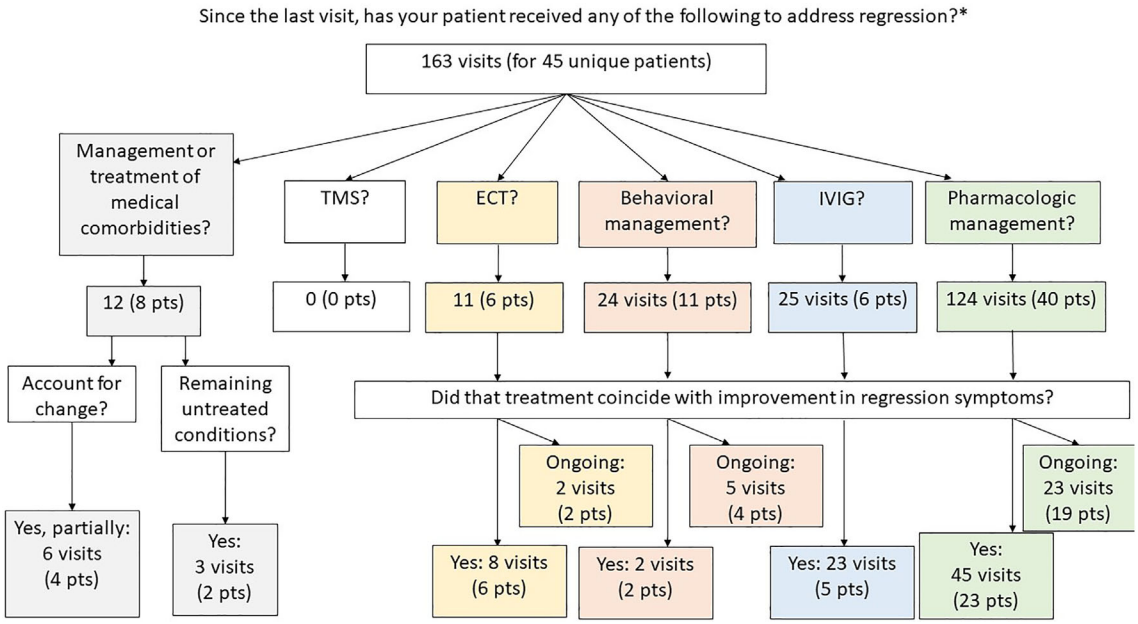

FIGURE 2 Management of patients with unexplained regression in Down syndrome (URDS), and if that management coincided with improvement in symptoms. Patients = pts; *Patients could receive more than one type of management at a single visit.

previously-reported (Santoro et al., 2020). This cohort had an average of 1.0 stressor, and 4.6 depression symptoms, which aligns with our published data on stressors and depression from data in the Appendix of Santoro et al (Santoro et al., 2020); cases with regression had 1.00 ± 1.06 stressors (controls had 0.17 ± 0.37) and cases with regression had 8.2 ± 6.6 depression symptoms (controls had 0.77 ± 1.59). Although the course of URDS varied, in this cohort, function tended to improve over subsequent visits to our DS specialty clinics with improvement occurring at 42% of visits. This may reassure families that clinicians' management is beneficial and provide some hope during difficult times. Indeed, studies to-date show improvement in catatonia with ECT and in DSDD with immunotherapy (Cardinale et al., 2018; Ghaziuddin et al., 2015). However, symptoms of URDS fully resolved in only 20% of patients suggesting that despite partial improvement, many patients may remain symptomatic and do not fully return to their premorbid function.

Pharmacologic and non-pharmacologic regimens at the time of improvement varied, consistent with the current literature (Ghaziuddin et al., 2015; Miles et al., 2019). Lorazepam, the first-line medication treatment for catatonia (Pelzer et al., 2018), was sometimes used at the time of improvement, along with other medications and non-pharmacologic management. Unlike previous studies (Cardinale et al., 2018; Ghaziuddin et al., 2015), our results are naturalistic and describe clinical management across sites which varied in prescribing dosages and intervals; we present successful regimens to inform clinicians. Practice variation may be due to clinical preference, access and experience at some sites. For example, Duke Medical Center uses IVIG clinically for DSDD, while IVIG is unavailable in Australia for URDS, and access to ECT can be variable. Improved reporting of the longitudinal course and response to treatment will inform future URDS research, and future studies could investigate the role of treatment bias in our results. For example, pharmacologic treatment occurred at 124 visits, while ECT and IVIG were at fewer, 11 and 25 visits, respectively. In the use of pharmacology, there are various medications and dosages to use, and pharmacology may be more readily available and commonplace for various physicians to order, while ECT and IVIG may be more specialized.

A clinician may ask which factors, if any, most predict the outcome in URDS. Although improvement was seen in multiple treatment modalities, in our analysis, the only factor significantly associated with higher rate of subsequent improvement was IVIG use ($p = 0.001$). Studies of IVIG have reported improvement in patients with DSDD (Cardinale et al., 2018; Hart et al., 2021; Worley et al., 2015). IVIG is usually well-tolerated, but can have side effects, and access may be limited by physician experience or local prescribing restrictions (Cherin et al., 2016). We present the IVIG protocols at the time of improvement (Table S2), as differences exist in IVIG infusion rates, dosages, and products (Cherin et al., 2016). Access to IVIG may be limited by physician experience or local prescribing restrictions. In our cohort, race of "Black", "Asian", "other" or "missing" was initially associated with higher rate of improvement in symptoms, but this was confounded by IVIG management. Future study could investigate this finding further and study IVIG dosing and side effects. Further, although IVIG was associated with inter-visit improvement, only one of the ten patients who had complete resolution was treated with IVIG; future research should investigate if IVIG leads to continued improvement in patients and eventual resolution of symptoms (Cherin et al., 2016). Future research could focus on the long-term impacts of

TABLE 4 Univariate analyses of the association between characteristics/types of management and improvement in symptoms from the previous visit in 45 patients with unexplained regression in Down syndrome (URDS) at 153 total visits; a subset of 27 patients with URDS and the feature of catatonia present

	Rate of improvement	*p*-value	Rate ratio (RR)	95% CI
Effect of baseline characteristics on rate on improvement				
Total cohort (N = 45)				
Sex				
Females	0.4887	0.2845	0.8365	0.6032–1.1600
Males	0.5842			
Race				
Non-white	0.6760	0.0301*	1.3125	1.0264-1.6781
White	0.5151			
Ethnicity				
Hispanic	0.6818	0.3340	1.2835	0.7735–2.1298
Non-Hispanic	0.5312			
Catatonia symptom				
Present	0.5470	0.9338	1.0154	0.7074–1.4575
Absent	0.5387			
Age at regression		0.4314	0.9891	0.9623–1.0165
Baseline URDS score		0.5626	0.9921	0.9660–1.0190
Baseline number of stressors		0.5393	0.9425	0.7801–1.1387
Baseline depression score		0.3498	1.0141	0.9847–1.0445
Effect of type of management on rate of improvement[a]				
Behavioral management				
Yes	0.6465	0.1508	1.2273	0.9281–1.6231
No	0.5268			
Pharmacologic management				
Yes	0.5383	0.5618	0.8885	0.5958–1.3248
No	0.6059			
ECT management				
Yes	0.6119	0.6371	1.1255	0.6886–1.8396
No	0.5436			
IVIG management				
Yes	0.8206	0.0014**	1.6360	1.2102–2.2117
No	0.5016			
Other management				
Yes	0.5911	0.7560	1.0813	0.6604–1.7704
No	0.5467			
Pharmacologic + ECT				
Yes	0.6119	0.6371	1.1255	0.6886–1.8396
No	0.5436			
Pharmacologic + IVIG				
Yes	0.7053	0.1516	1.3246	0.9020–1.9452
No	0.5324			
Catatonia present cohort (N = 27)				
Effect of type of management on rate of improvement[b]				
Behavioral management				
Yes	0.6365	0.1706	1.2012	0.9241–1.5613
No	0.5299			

(Continues)

TABLE 4 (Continued)

	Rate of improvement	*p*-value	Rate ratio (RR)	95% CI
ECT management				
Yes	0.5870	0.7730	1.0769	0.6508–1.7820
No	0.5451			
Pharmacologic + ECT management				
Yes	0.5870	0.7730	1.0769	0.6508–1.7820
No	0.5451			

Note: *p < 0.01–0.05; **p < 0.01.

[a]No patients had IVIG + ECT or IVIG + behavioral at the same visit, and only 2 had behavioral + pharm + ECT at the same visit, which is not sufficient for statistical analysis.

[b]In the catatonia present group, stability was present in some of the models due to very low number of visits with certain treatments, so only treatments that were reported for at least 10 visits are included. Note that pharmacologic treatment alone is not included because there were fewer than 10 visits where it was not used.

IVIG in URDS, and basic science research analyzing the etiology of URDS and the mechanism by which IVIG leads to clinical improvement.

Limitations to this study lie in its retrospective, naturalistic multi-site design that could include subtle differences between sites; we sought to describe the longitudinal, medical management that patients with URDS receive and to use a standard functional measure in REDCap to reduce heterogeneity. There are likely differences between centers which persist despite our efforts to harmonize data. For example, we found that more patients in Australia had catatonia as a feature than patients in Italy. This could be due to chance or due to differences in referral patterns in the two countries due to differences in clinic model, specialty of lead at clinic site, or other differences in hospital systems. Additionally, although we followed patients over time, we chose when to review charts and our endpoint on data collection was arbitrary; clinical improvement might still occur for patients after the time of chart review. We had a high degree of variability in the number of visits; some of this may be based on differences in clinic model or specialty of sites in our consortium—for example, some teams may have patients back frequently to monitor treatment with IVIG while other clinical models involve referral to psychiatry and annual check-ins with the medical team. Some of our patients had only one or two visits, and further details may be unknown, such as whether they had a robust treatment response without a need to return for follow-up, whether they were dissatisfied with treatment, whether they moved away, or whether they sought out an expert consultation with local follow-up for management. Due to the nature of patients not returning, we do not have follow-up information to answer some of these questions, nor are we able to compare those that continued to follow with our sites versus those that did not. A clinical trial with high research retention could be considered in the future to address some of these questions.

Validated, longitudinal, objective measures for URDS and catatonia are lacking for individuals with intellectual disability. In our consortium's experience, existing measures can produce false positive scores (for example, scoring for mutism in a patient who is nonverbal, or scoring for automatic obedience due to difficulty following verbal instructions). Therefore, we created two measures, the Parent-reported Functional Score and the Clinician-administered Functional Assessment. Although an important, real-world indicator of meaningful change to families, reporting and recall bias may occur. In some instances, the first visit to one of our DS clinics could have occurred over a year after the beginning of symptoms, and much of the data collected relied on parent recall. In the future, adding clinician-report items about medication and treatment choice, using existing standardized measures, such as the Clinician Global Impression of Change, or developing a standardized, validated, objective outcome measure would enhance our research.

Future studies should build on our preliminary results through a standardized management algorithm of specific treatments, or treatment protocol. Ideally, a clinical trial designed to compare and contrast each treatment modality powered to evaluate management which has been shown effective in the literature, but not of statistical significance in our sub-analysis, such as ECT and lorazepam, or management not seen in our cohort, such as TMS. Our descriptive, real-world data could lay the groundwork to for future researchers to develop a clinical practice guideline for URDS.

5 | CONCLUSION

In patients with URDS, the longitudinal course varies. At the time of parent-reported improvement, clinical management included medications, IVIG, and ECT. Comparing rates of improvement, IVIG management was associated with higher rate of improvement at the subsequent visit though the sample size for IVIG was small; even though there were more visits and this reached statistical significance. This ecological clinical cohort lays the groundwork for future rigorous clinical research.

AUTHOR CONTRIBUTIONS

Dr. Santoro wrote the original draft, participated in formal data analysis, participated in conceptualization, planning the methodology, project administration and conducted the investigation, collecting data

and contributed to the scientific writing - review and editing, and created figures and data visualization; Ms. Horick conducted in formal data analysis, and contributed to the scientific writing - review and editing; Ms. Krell created figures and data visualization, participated in conceptualization, planning the methodology, project administration and conducted the investigation, collecting data, reviewing the formal data analysis, and contributed to the scientific writing - review and editing; Dr. Sargado, Dr. Baumer, Ms. Hojlo, Ms. Milliken, and Ms. Pawlowski created figures and data visualization, participated in conceptualization, planning the methodology, project administration and conducted the investigation, collecting data, reviewing the formal data analysis, and contributed to the scientific writing - review and editing; Dr. Cornachia, Dr. Franklin, Dr. Hart, Ms. Haugen, Dr. Kishnani, Dr. McCormick, Dr. Oreskovic, Ms. Torres, Dr. Valentini, Dr. Vellody participated in conceptualization, planning the methodology, project administration and conducted the investigation, collecting data, reviewing the formal data analysis, and contributed to the scientific writing - review and editing; Dr. Skotko supervised the overall project, participated in conceptualization, planning the methodology, project administration and conducted the investigation, collecting data and contributed to the scientific writing - review and editing; All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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No funding was secured for this study.

CONFLICT OF INTEREST

SLS has received research funding from LuMind Research Down Syndrome Foundation to conduct clinical trials for people with Down syndrome within the past 2 years. She serves in a non-paid capacity on the Medical and Scientific Advisory Council of the Massachusetts Down Syndrome Congress, the Board of Directors of the Down Syndrome Medical Interest Group (DSMIG-USA), and the Executive Committee of the American Academy of Pediatrics Council on Genetics.

CF does not receive funding for this work; but does receive funding for a separate project about DS catatonia from the BICARE Foundation.

BGS occasionally consults on the topic of Down syndrome through Gerson Lehrman Group. He receives remuneration from Down syndrome non-profit organizations for speaking engagements and associated travel expenses. Dr. Skotko receives annual royalties from Woodbine House, Inc., for the publication of his book, *Fasten Your Seatbelt: A Crash Course on Down Syndrome for Brothers and Sisters*. Within the past 2 years, he has received research funding from F. Hoffmann-La Roche, Inc., AC Immune, and LuMind Research Down Syndrome Foundation to conduct clinical trials for people with Down syndrome. Dr. Skotko is occasionally asked to serve as an expert witness for legal cases where Down syndrome is discussed. Dr. Skotko serves in a non-paid capacity on the Honorary Board of Directors for the Massachusetts Down Syndrome Congress and the Professional Advisory Committee for the National Center for Prenatal and Postnatal Down Syndrome Resources. Dr. Skotko has a sister with Down syndrome.

The other authors do not have any conflicts to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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