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ORIGINAL PAPER

Repetitive and Self-injurious Behaviors in Children with Cornelia de Lange Syndrome

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Abstract

Cornelia de Lange syndrome (CdLS) is associated with repetitive and self-injurious behaviors (RBs, SIB). Evaluating children with CdLS, this study: (1) characterizes the spectrum of RBs; (2) characterizes the impact and severity of RBs including SIB; (3) describes how age and adaptive functioning relate to RBs including SIB. Fifty children (5–17 years) with CdLS were assessed with Children's Yale-Brown Obsessive Compulsive Scale Modified for PDD; Aberrant Behavior Checklist (ABC); Vineland Adaptive Behaviors Scales (VABS). All children had ≥ 1 type of RB; 44% had some form of SIB. 64% spent > 1 h/day displaying RBs. Lower VABS adaptive functioning was associated with higher stereotypy and SIB scores (ABC). In children with CdLS, RBs including SIB are common, impactful, and associated with lower adaptive functioning.

Keywords Cornelia de Lange syndrome · Repetitive behaviors · Stereotypies · Self-injurious behaviors

Introduction

Repetitive clinical phenomena are common in children and adults with developmental disabilities, comprising a spectrum of clinical manifestations which include motor stereotypies (simple motor movements with no apparent functional value), complex repetitive motor sequences (such as spinning, running), and compulsions (cognitively driven repetitive behaviors). The sum of these behaviors can be construed as repetitive behaviors (RBs), while a critical subset of RBs is comprised by self-injurious behaviors (SIB). SIB can be considered an extension of motor stereotypies causing bodily harm in topographically defined body areas (e.g., self-hitting targeting the head, self-biting of the hand). Ultimately, RBs, and particularly SIB, are areas of significant clinical concern for families and patients.

Cornelia de Lange syndrome (CdLS) is a rare genetic disorder associated with somatic, cognitive, and behavioral deficits. In over half of affected individuals, CdLS is caused by pathogenic variants in *NIBPL* (Gillis et al. 2004), which encodes a major constituent of the cohesin complex. The cohesin complex is critical for cell division, and the NIPBL protein product also plays a role in the regulation of developmental gene systems, including neurodevelopment (Kawauchi et al. 2009; van den Berg et al. 2017). CdLS can be caused by mutations in other cohesin-related genes, such as *SMC1A*, *SMC3* (Deardorff et al. 2007), and *HDAC8* (Deardorff et al. 2012), among others. The clinical syndrome of CdLS includes distinct facial features, microcephaly, short stature, and limb abnormalities (Kline et al. 2018). Neuropathological changes include cerebral atrophy, white matter changes, cerebellar hypoplasia, and enlarged ventricles (Roshan Lal et al. 2016).

Children with CdLS have a range of intellectual disability (ID), as well as maladaptive behavioral traits, such as

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hyperactivity (Basile et al. 2007), autistic features (Moss et al. 2012; Srivastava et al. 2014), unstable or low mood states (Nelson et al. 2014), and catatonia-like behaviors (Bell et al. 2018). RBs including SIB are common in CdLS: within this syndrome, the prevalence of stereotypies is 42% (Hyman et al. 2002), the prevalence of compulsive behaviors is 87% (Oliver et al. 2008), and the prevalence of SIB is as high as 70% (Arron et al. 2011). Prior work has characterized the phenomenology of RBs in CdLS (children and adults) in comparison with other genetic syndromes using the Repetitive Behavior Questionnaire (among other measures) (Moss et al. 2009; Watkins et al. 2019). Specific RBs seen in CdLS in contrast to other disorders include tidying up and lining up behaviors (Moss et al. 2009). Compared to idiopathic autism, children with CdLS exhibit less RBs (specifically sensory interests) based on the Autism Diagnostic Observation Schedule (Moss et al. 2012). Compared to individuals with ID matched in terms of age, sex, wheelchair use, and adaptive skills, children and adults with CdLS exhibit higher levels of compulsive behaviors based on the Compulsive Behavior Checklist (Oliver et al. 2008). With respect to the phenomenology of SIB in CdLS, in comparison with ID of heterogeneous etiology, individuals with CdLS (children and adults) have higher levels of body self-hitting and self-pulling (Arron et al. 2011). Notably, SIB in CdLS tends to occur in more severely affected individuals in association with other RBs (Arron et al. 2011; Basile et al. 2007).

However, more information is needed about the RB and SIB profile of *children* with CdLS, given that many of these aforementioned studies have involved both children and adults with CdLS. Further, there needs to be more exploration of specific types of compulsive behaviors in CdLS. Finally, additional exploration of the impact of RBs including SIB on daily life for affected individuals/caregivers is warranted. To fully characterize the type, impact, and associated features of RBs including SIB in a large cohort of children with CdLS, the current report (1) characterizes specific types of RBs including compulsive behaviors; (2) assesses the clinical impact of RBs including SIB through standardized ratings; and (3) describes how age and adaptive functioning relate to RBs including SIB. One of the main novelties of this work lies in its exploration of the impact of RBs including SIB on daily life for affected individuals/caregivers, an area of much needed exploration as it pertains to CdLS.

Methods

Study Population

Children with CdLS ages 5–17 years were recruited through advertisements and during national CdLS Foundation meetings, as detailed previously (Srivastava et al. 2014). Subjects had a clinical diagnosis of CdLS but were not required to have confirmatory molecular testing. Although an underlying genetic cause is detected in 50–70% of clinical diagnoses (Boyle et al. 2015; Gillis et al. 2004), a substantial number of subjects (n = 32) were enrolled in 2004, when gene testing for *NIPBL* (much less other genes associated with CdLS) was not commercially available. Parent/caregiver-report questionnaires were completed by mail. Interview questionnaires were completed either on site or by phone. Written informed consent from all parents or caregivers was obtained. The protocol was approved by the Institutional Review Board. All interview-based instruments were completed by an experienced board-certified child psychiatrist (MAG).

Measures

The Children's Yale-Brown Obsessive Compulsive Scale Modified for Pervasive Developmental Disorders (CY-BOCS-PDD) is a clinician-rated, semi-structured interview intended to assess repetitive compulsion symptoms and severity, adapted specifically for children (Scahill et al. 2006). The CY-BOCS-PDD has items pertaining to RBs across 9 categories: washing/cleaning, checking, repeating, counting, ordering/arranging, hoarding/saving, excessive games/superstitious behaviors, rituals involving other persons, and miscellaneous. Distinct from the CY-BOCS, the CY-BOCS-PDD repeating category includes: touching in patterns, rocking, spinning, twirling, pacing, spinning objects, and echolalia. Severity is evaluated across five dimensions: time spent performing the behaviors, interference due to the behaviors, distress associated with the behaviors, amount of effort made to resist against the behaviors, and degree of control over the behaviors. Each severity item is rated from 0 to 4 (none-extreme), with a total possible severity score of 20. The CY-BOCS-PDD has high internal consistency (alpha = 0.85) and reliability (intraclass correlation coefficient = 0.97) The CY-BOCS-PDD has been validated in children (5–17 years of age) with (as described in prior nomenclature) autism, Asperger disorder, and PDD-not otherwise specified, including those with ID. Comparison of ID to no ID in this validation work has shown similar internal consistency between the two groups. Though the performance of the CY-BOCS-PDD was different between the groups, the differences were, for the most part, not statistically significant (Scahill et al. 2006).

The Aberrant Behavior Checklist (ABC) is a normed 58-item self-report caregiver checklist for individual with ID that assesses problem behaviors occurring in the previous month (Aman et al. 1986). The checklist comprises five subscales: (a) irritability (mood lability, self-injury, aggression); (b) lethargy/social withdrawal (isolation from others,

little interaction); (c) stereotypies; (d) hyperactivity; and (e) abnormal speech. Each individual item in the checklist is rated as yes/no; if positive, a severity score is obtained (0 = not a problem; 1 = slight problem; 2 = moderately serious problem; 3 = severe problem). For each of the five subscales, we generated a scaled subscale score, equal to the total score in that subscale divided by the number of items in the subscale, in order to facilitate cross-subscale comparisons. To better characterize SIB using the ABC, a composite ABC SIB score was generated based on the average of responses to three ABC questions (question 2: injures self on purpose; question 50: deliberately hurts self; and question 52: does physical violence to self). The ABC's internal consistency is high (0.86–0.94), its inter-rater reliability is moderate to high (0.17–0.90), and its test–retest reliability is high (0.96–0.99). It demonstrates adequate predictive validity, moderate divergent validity with several adaptive behavior scales, and convergent validity with observations of behavior (Aman et al. 1986).

The Vineland Adaptive Behaviors Scales (VABS) is a structured interview designed to assess adaptive behavior across four domains of functioning: (a) communication; (b) activities of daily living (ADL); (c) socialization; and (d) motor skills (Sparrow et al. 1984). Children with raw VABS scores below threshold for standard score determination (i.e., floor effect) were assigned standard scores of 20 for each domain (lowest standard score 20). The VABS's internal consistency is moderate to high (split half means for domains 0.83–0.90 and for Adaptive Behavior Composite 0.94), its test–retest reliability is moderate (0.81–0.86 for domains and 0.88 for Adaptive Behavior Composite), and its inter-rater reliability is moderate (0.62–0.78 for domains and 0.74 for Adaptive Behavior Composite). In addition, it is reported to have content validity, construct validity, and concurrent validity (Sparrow et al. 1984). Of note, initial data collection occurred before introduction of the second edition of the VABS in 2006.

The Diagnostic Criteria for Cornelia de Lange Syndrome (DC-CdLS) is a medical criteria checklist which describes the somatic features of CdLS. Following accepted guidelines, major criteria (growth, development, and behavior) and minor criteria (hirsutism, facial features, extremity findings, and neurosensory system issues) were used to ascertain a diagnosis of CdLS (Kline et al. 2007). Participant enrollment and data collection occurred prior to publication of updated CdLS diagnostic criteria (Kline et al. 2018).

The Clinical Classification and Diagnosis of CdLS

There were several criteria used to ascertain a clinical diagnosis of CdLS for each participant. First, all children enrolled in this study had already been diagnosed clinically by a geneticist. For some children (n = 21), confirmation was made by a clinical geneticist with specific expertise in CdLS (ADK). Second, for all children, analysis of photographs of facial and limb features was performed (ADK). Third, a small fraction of the cohort (n = 9) had pathogenic variants in *NIPBL*; the others either did not have genetic testing for CdLS related mutations, or results were unavailable for review. Fourth, each participant satisfied diagnostic criteria based on the DC-CdLS checklist. For all participants, final diagnoses were reviewed by ADK.

Data Analysis

Frequencies were tabulated for categorical data in descriptive analyses. For comparisons involving parametric independent variables, t-test was used. For correlations between two ordinal variables, or between an ordinal and a quantitative non-normal variable, Spearman's rank correlation was used. For correlations between an ordinal and a quantitative normal variable, linear regression was used, with reporting of coefficients and confidence intervals. In examining the relationships among RBs, SIB, and functioning and severity, significance was set at $p < 0.05$ (two-sided).

Results

Participant Sample

Fifty children with CdLS were included in the study, with ages ranging from 5 to 17 years of age (11.2 ± 3.8 years). Over half, 26/50 (52%), were female. Based on the DC-CdLS Checklist, 39/50 (78%) had gastroesophageal reflux disease (GERD), while 2/50 (4%) had malrotation/volvulus and 2/50 (4%) had another severe gastrointestinal (GI) malformation. Seizures were present in 10/50 (20%), and 23/50 (46%) had congenital heart defects. There was no statistically significant difference by sex in any of the repetitive behavior measures (CY-BOCS-PDD severity items, scaled ABC stereotypy score, or scaled composite ABC SIB score) or adaptive measures (VABS scores), except for total number of RBs, which was greater in females ($t = 2.08$, $p = 0.04$) (Table 1).

Spectrum of Repetitive Behaviors

A spectrum of RBs were present in the cohort of children with CdLS. All 50 participants had at least one RB based on the CY-BOCS-PDD. The three most prevalent RB types were: *repeating* behaviors (at least one of which was present in n = 39, 78%), *miscellaneous* behaviors (at least one of which was present in n = 32, 64%), and *washing* behaviors (at least one of which was present in n = 22, 44%). The *repeating* behaviors category in the CY-BOCS-PDD

Table 1 Repetitive behaviors and adaptive measures in the cohort

Measure	Male (n = 24)	Female (n = 26)	Entire Cohort (n = 50)
CY-BOCS-PDD			
Total number of repetitive/compulsive behaviors*	3.7 ± 2.1	4.9 ± 1.9	4.3 ± 2.1
Time severity score[a]	2.0 ± 0.8	1.7 ± 1.0	1.9 ± 0.9
Interference rating[a]	1.8 ± 1.0	1.4 ± 1.2	1.6 ± 1.1
Distress rating[a]	2.3 ± 0.9	2.1 ± 1.0	2.2 ± 0.9
Resistance rating[a]	3.0 ± 1.1	3.4 ± 1.1	3.2 ± 1.1
Degree of control rating[a]	2.8 ± 1.1	3.2 ± 1.3	3.0 ± 1.2
ABC			
Scaled stereotypy subscale[b]	0.6 ± 0 .7	0.5 ± 0.5	0.6 ± 0.6
Stereotypy subscale (not scaled)[c]	4.5 ± 5.0	3.3 ± 3.7	3.9 ± 4.3
Scaled composite SIB score[b]	0.9 ± 1.1	0.9 ± 1.1	0.9 ± 1.0
Composite SIB score (not scaled)[d]	2.8 ± 3.2	2.6 ± 3.2	2.7 ± 3.1
VABS			
Composite standard score[e]	39.8 ± 24.0	37.8 ± 16.9	38.7 ± 20.4
Socialization standard score[e]	52.4 ± 24.4	50.9 ± 20.9	51.6 ± 22.4
Communication standard score[e]	43.4 ± 26.2	38.8 ± 18.9	41.0 ± 22.6
Activities of daily living standard score[e]	34.6 ± 25.9	34.7 ± 19.3	34.7 ± 22.5

CY-BOCS-PDD Children's Yale-Brown Obsessive Compulsive Scale Modified for Pervasive Developmental Disorders, *ABC* Aberrant Behavior Checklist; *VABS* Vineland Adaptive Behaviors Scales

[a]Possible values for severity scores range from 0 to 4; higher scores reflect higher severity

[b]Possible values for scaled scores range from 0 to 3; higher scores reflect increased severity

[c]Possible values for Stereotypy subscale score range from 0 to 21

[d]Possible values for composite SIB score range from 0 to 9

[e]VABS subdomain scores are normalized such that mean = 100 and one standard deviation = 15; higher scores reflect better adaptive functioning

*p = 0.04 when comparing males and females

includes complex and simple stereotypies, while the *miscellaneous* behaviors category includes hair-pulling, skin picking, and other self-damaging behaviors. Among those with washing behaviors, n = 17 (34%) engaged in repetitive water play. Within the CY-BOCS-PDD *miscellaneous* category, 10/50 (20%) had trichotillomania and/or skin picking, while 17/50 (34%) had other self-damaging or self-mutilating behaviors. Notably, the total number of children who had any SIB (trichotillomania, skin picking, or other self-damaging or self-mutilating behaviors) based on the CY-BOCS-PDD was 22/50 (44%) (Table 2).

Repetitive Behaviors are Clinically Impactful

A significant clinical impact was associated with RBs in children with CdLS. The average number of repetitive/compulsive behaviors exhibited by each child was 4.3 ± 2.1 (range 1–9; Fig. 1). The five CY-BOCS-PDD severity item scores are shown in Table 1. The average rating for "time spent" by each child performing RBs was 1.9 ± 0.9 (1 = < 1 h/day; 2 = 1–3 h/day), suggesting that on average most children spend close to 1–3 h of the day engaging in RBs. Of the total sample, 32/50 (64%) had a CY-BOCS-PDD time severity score of ≥ 2, in the clinically significant range of > 1 h per day engaging in RBs. The mean rating for interference due to RBs was 1.6 ± 1.1 (1 = mild/slight interference; 2 = moderate/definite interference). Of the total sample, 39/50 (78%) had a CY-BOCS-PDD distress severity score of ≥ 2 (2 = moderate/mounting anxiety or frustration but within a manageable range). Average severity ratings for patient resistance against RBs by parental report (3 = severe) and degree of control over RBs by parental report (3 = little control) were both above 3. The total CY-BOCS-PDD severity score (total of severity scores 1–5) was 11.8 ± 3.9.

Stereotypies

Motor stereotypies, as characterized by the ABC, had varying degrees of impact on functioning. The majority of children, 37/50 (74%), had a scaled ABC stereotypy subscale score < 1 (1 = slight problem). Of the total sample, 12/50 (24%) had a scaled ABC stereotypy subscale score of 1–2 (slight-moderate problem), and only 1/50 (2%) had a scaled stereotypy subscale score ≥ 2 (moderate or higher problem). Within the scaled ABC stereotypy subscale, the highest scored individual items were those describing

Table 2 Prevalence of specific repetitive/compulsive behaviors in the cohort based on the Children's Yale-Brown Obsessive Compulsive Scale Modified for Pervasive Developmental Disorders

Category	Number of patients with compulsion (% of cohort)
Washing/cleaning compulsions	22 (44%)
Handwashing	1 (2%)
Showering, bathing, toothbrushing, grooming, toilet routine	4 (8%)
Cleaning of items	0 (0%)
Repetitive water play	17 (34%)
Other measures to prevent/remove contact with contaminants	1 (2%)
Other	0 (0%)
Checking compulsions	15 (30%)
Checking locks, toys, school books/items	6 (12%)
Checking associated with getting washed, dressed, undressed	0 (0%)
Checking that did not/will not harm others	0 (0%)
Checking that did not/will not harm self	0 (0%)
Checking that nothing terrible did/will happen	0 (0%)
Checking that did not make mistake	1 (2%)
Checking tied to somatic obsessions	0 (0%)
Other	9 (18%)
Repeating rituals	39 (78%)
Rereading or rewriting	0 (0%)
Need to repeat routine activities	9 (18%)
Touching in patterns	6 (12%)
Rocking	11 (22%)
Spinning, twirling, pacing	18 (36%)
Spinning objects	6 (12%)
Echolalia	10 (20%)
Other	18 (36%)
Counting compulsions	2 (4%)
Objects, certain numbers, words, etc	2 (4%)
Other	0 (0%)
Ordering/arranging	16 (32%)
Need for symmetry or ordering up	16 (32%)
Other	2 (4%)
*Hoarding/saving compulsion*s	14 (28%)
Difficulty throwing things away, saving bits of paper, string	12 (24%)
Other	2 (4%)
Excessive games/superstitious behaviors	0 (0%)
Rituals involving other persons/parents	14 (28%)
Repetitive requests or demands	7 (14%)
Other	8 (16%)
Miscellaneous compulsions	32 (64%)
Mental rituals	0 (0%)
Need to tell, ask, or confess	6 (12%)
Measures to prevent harm to self	0 (0%)
Ritualized eating behaviors	3 (6%)
Repetitive sexual behavior	1 (2%)
Excessive list making	0 (0%)
Rituals involving blinking or staring	0 (0%)
Trichotillomania, skin picking	10 (20%)
Other self-damaging or self-mutilating	17 (34%)
Other	11 (22%)

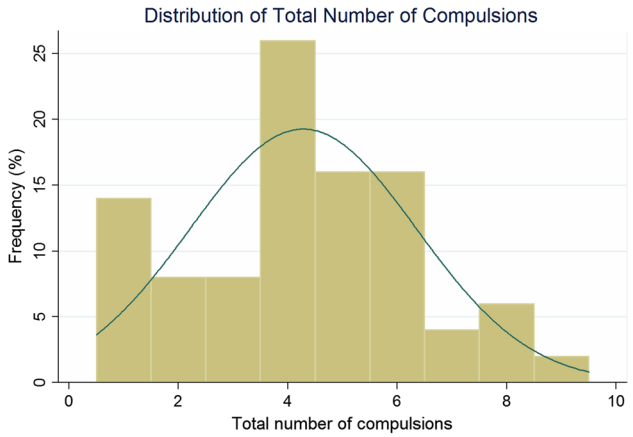

Fig. 1 Distribution of total number of repetitive/compulsive behaviors in the cohort. The total number of behaviors is the sum of individual items on the Children's Yale-Brown Obsessive Compulsive Scale Modified for Pervasive Developmental Disorders

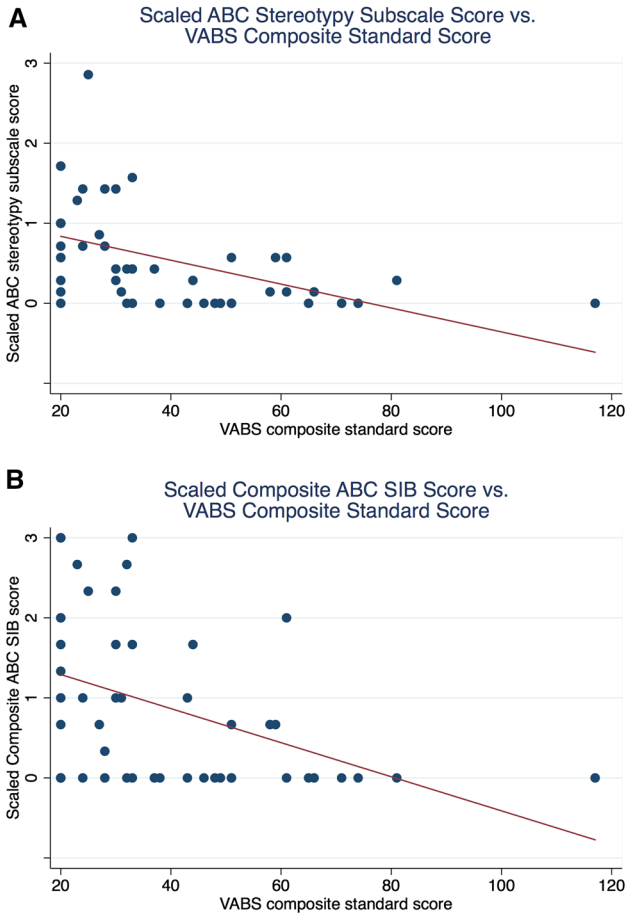

Fig. 2 Stereotypy and self-injurious behaviors (SIB) scores versus adaptive functioning in the cohort. The x-axis is the Vineland Adaptive Behavior Scales (VABS) composite standard score (higher score = better adaptive functioning). In **a**, the y-axis is the scaled Aberrant Behavior Checklist (ABC) stereotypy subscale score (higher score = greater severity). In **b**, the y-axis is the scaled composite ABC SIB score

stereotyped behavior/abnormal repetitive movements (0.9 ± 1.0, range 0–3); repetitive hand, body, or head movements (0.7 ± 0.9, range 0–3); and meaningless, recurring body movements (0.7 ± 0.8, range 0–3). Lower rated items included odd, bizarre in behavior (0.6 ± 0.8, range 0–3); waves or shakes extremities repeatedly (0.5 ± 0.9, range 0–3); rocks body back and forth repeatedly (0.3 ± 0.8, range 0–3); and moves or rolls head back and forth repetitively (0.1 ± 0.5, range 0–2).

Self-Injurious Behaviors

Over half of the cohort, 29/50 (58%), had a scaled composite ABC SIB score < 1, while 21/50 (42%) had a scaled composite ABC SIB score ≥ 1 (slight problem or worse). With respect to higher score ranges, 10/50 (20%) had a scaled composite ABC SIB score between 1 and 2 (slight-to-moderate problem), while 7/50 (14%) had scores between 2 and 3 (moderate-to-severe problem). Finally, 4/50 (8%) had a score of 3 (severe problem).

Relationship of Stereotypies and Self-Injurious Behaviors to Various Factors (Adaptive Functioning, Clinical Severity, Age, Health Status)

There was a statistically significant inverse correlation between scaled ABC stereotypy scores and VABS adaptive functioning composite standard scores (Spearman's rho $= -0.61$, $p < 0.0001$) (Fig. 2a). In fact, scaled ABC stereotypy scores were significantly correlated with all VABS subscales, including lower socialization standard scores (adjusted $R^2 = 0.19$, $p = 0.001$), lower communication standard scores (Spearman's rho $= -0.59$, $p < 0.0001$), and lower activities of daily living standard scores (Spearman's rho $= -0.59$, $p < 0.0001$).

When examining the association of SIB with VABS adaptive functioning, a similar pattern emerged: there was a statistically significant correlation between higher scaled composite ABC SIB scores and lower VABS composite standard scores (Spearman's rho $= -0.44$, $p = 0.002$, Fig. 2b), lower VABS socialization standard scores (adjusted $R^2 = 0.13$, $p = 0.005$), lower VABS communication standard scores (Spearman's rho $= -0.42$, $p = 0.003$), and lower VABS activities of daily living standard scores (Spearman's rho $= -0.49$, $p = 0.0003$). Thus, the data suggest a relationship between both stereotypies and SIB with adaptive skills in children with CdLS, though the directionality of this relationship is not clear.

There was no significant correlation between age and scaled ABC stereotypy subscale scores (Spearman's

rho = 0.16, p = 0.27) or scaled composite ABC SIB scores (Spearman's rho = 0.19, p = 0.18). In addition, somatic features of CdLS (GER, diaphragmatic hernia, malrotation/volvulus, other severe GI malformation, seizures, heart defect) were not related to scaled ABC stereotypy subscale scores (Spearman's rho = 0.14, p = 0.35 specifically for GER) or scaled composite ABC SIB scores (Spearman's rho = 0.04, p = 0.77 specifically for GER). Finally, the correlation of scaled ABC stereotypy subscale scores with scaled composite ABC SIB scores showed that higher severity of stereotypies is associated with higher severity of SIB (Spearman's rho = 0.38, p = 0.007) (Fig. 3).

Discussion

The current report details repetitive clinical phenomena in a large cohort of children with CdLS through several key findings. RBs are found to be extremely common in children with CdLS. Notably, the presence of stereotypies is a risk factor for SIB in this cohort. RBs are also found to be clinically impactful in children with CdLS, with parents reporting significant interference with daily activities. Finally, a lower level of adaptive functioning is strongly associated with RBs including SIB in children with CdLS.

Repetitive Behaviors are Common in Children with CdLS

The current data suggest that RBs are common in children with CdLS. Based on the CY-BOCS-PDD, 100% of our cohort demonstrated *at least* one RB. Most prevalent were "repeating" behaviors, including repetitive body movements, such as spinning, twirling, pacing, and rocking behaviors.

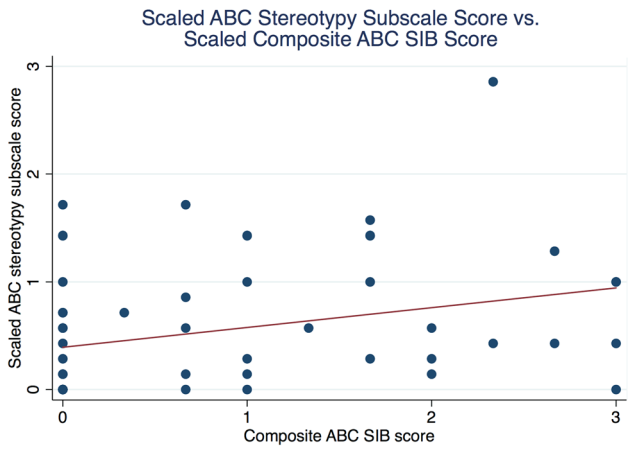

Fig. 3 Scaled Aberrant Behavior Checklist (ABC) stereotypy subscale score versus scaled composite ABC self-injurious behaviors (SIB) score in the cohort

Close to half of the cohort had at least one repetitive "washing" behavior; in particular, repetitive water play was noted. This trait is not necessarily specific to CdLS, as it can be seen in other genetic syndromes, such as Angelman syndrome, as well as in non-syndromic ID (Didden et al. 2008). SIB was present in 27/50 (44%) of children as rated by the CY-BOCS-PDD. Based on the CY-BOCS-PDD, notable SIB in children with CdLS include trichotillomania, skin picking, and other self-damaging or self-mutilating behaviors. These specific RBs can be catalogued as grooming disorders and have served as a model for disorders associated with impulse control deficits, amenable to therapies that use the habit reversal therapy (HRT) paradigm (Bate et al. 2011).

The current data are consistent with prior reports suggesting the common occurrence of RBs in CdLS (Hyman et al. 2002; Moss et al. 2009). A prior case–control study of 54 individuals with CdLS revealed that 87% of the CdLS group had at least one kind of compulsive behavior based on the Compulsive Behavior Checklist, in contrast to 58% of the comparison group, which consisted of 46 individuals with ID (Oliver et al. 2008). Likewise, in another study, the prevalence of self-injury was 56% in the CdLS group versus 41% in a comparison group (Oliver et al. 2009). Other studies have reported SIB rates as high as 70% (Arron et al. 2011; Hyman et al. 2002) in individuals with CdLS. Thus, repetitive clinical phenomena are consistently found in CdLS in prior literature, confirmed here in a large cohort of pediatric CdLS. RBs span across multiple developmental disorders and are found at significant rates in Angelman syndrome, Cri du chat syndrome, Fragile X syndrome, Prader–Willi syndrome, Lowe syndrome, and Smith–Magenis syndrome (Moss et al. 2009). SIB are also common in these populations, with one study reporting SIB rates of 55% in Fragile X syndrome, 18% in Down syndrome, and 50% in autism (Richards et al. 2012).

The severity of motor stereotypies correlated with the severity of SIB in the current report. While this association suggests an underlying common biological mechanism to both non-SIB motor stereotypies and frank SIB, it should be noted that modulating environmental factors of SIB (response to cues of social attention or need for escape from demands) were not measured in the current data. Likewise, it may be difficult to distinguish SIB which appear to occur *in vacuo* (in the "alone" condition in behavior paradigms) from those that respond to operational conditions. Ultimately, the importance of this distinction lies in that the social attention and demand conditions are amenable to manipulation of SIB frequency through behavioral interventions, whereas the SIB occurring in the context of the "alone" condition may be more responsive to pharmacological manipulation. The relationship of SIB to other types of repetitive phenomena, such as stereotypies and compulsive behaviors, is an area of intense inquiry (Symons et al. 2005; Richman and

Lindauer 2005; Matson and Nebel-Schwalm 2007). While some reports suggest clinical differences between SIB and stereotypies (Medeiros et al. 2013), other reports clearly note that SIB rarely occurs without concomitant non-SIB stereotypies in individuals with ID, with some authors noting that SIB is a "more severe form of stereotyped movements" (Gal et al. 2009). The association of non-SIB RBs and SIB occurs across genetic conditions. Individuals with Fragile X syndrome, Prader-Willi syndrome, and Lowe syndrome demonstrate non-SIB repetitive and impulsive behaviors, which are closely associated with SIB (Arron et al. 2011). Finally, from a developmental perspective, stereotypies early in life temporally precede SIB, with the age of onset of stereotypies documented around 19 months of age and the onset of SIB occurring at approximately 24 months (Richman and Lindauer 2005). Further research is needed to elucidate a possible pathophysiological connection between non-SIB repetitive phenomena and frank SIB, and examine if the emergence of the early RBs may signal a risk factor, and an opportunity for intervention, for later, more disabling SIB.

Repetitive Behaviors in Children with CdLS Have a Strong Clinical Impact

RBs in CdLS have a significant functional impact. Based on the CY-BOCS-PDD, over half of children with CdLS in the current study (32/50, 64%) spent > 1 h per day engaged in repetitive phenomena, and the associated distress rating noted mounting anxiety or frustration in the child related to these behaviors. Based on the ABC, motor stereotypies were a slight problem or worse for approximately one-quarter (13/50, 26%) of the cohort, while SIB were a slight problem or worse for just under half (21/50, 42%) of the cohort.

The difference in perceived impact between motor stereotypies and SIB is not surprising. Whereas repetitive head, extremity, or body movements may be harmless and perceived as such, SIB are not clinically benign and are considered to be far more distressing. In other words, SIB of varying degrees of severity is commonly present in children with CdLS in the current data, resulting in a serious clinical concern that increases family and treatment burden for a subgroup of children. SIB requires close monitoring due to the resultant functional disability, impairment, and distress to those suffering and their families, as well as the need for specialized treatment programs (Doehring et al. 2014).

The total CY-BOCS-PDD score—representing collective impact of repetitive compulsive behaviors—in our cohort was 11.8, which is reduced compared to that reported in the validation cohort of the CY-BOCS-PDD (14.4 ± 3.86) comprising individuals with autism, Asperger disorder, and PDD-not otherwise specified (Scahill et al. 2006). This result is somewhat surprising, given expectation that individuals with CdLS are particularly affected from a behavioral perspective. However, in support of this, at least one prior study has shown that children with CdLS exhibit less RB than children with idiopathic autism (Moss et al. 2012). Alternatively, severity item 4 and 5 in CY-BOCS-PDD (pertaining to resistance against compulsions and degree of control over compulsive behavior, respectively) may be more difficult to interpret in children with severe communication impairment as is the case for many in our sample, which may skew total CY-BOCS-PDD scores.

Repetitive Behaviors in Children with CdLS are Associated with a Lower Level of Adaptive Functioning

Consonant with prior reports on predisposing factors for RB including SIB, lower adaptive functioning—a proxy for ID—is significantly associated with both stereotypies ($p < 0.0001$) and SIB ($p = 0.002$). In line with these findings, a survey on almost 700 residents in a group home for individuals with ID identified SIB with self-restraint only in severe-to-profound ID individuals (Fovel et al. 1989). A state-wide survey on over 1300 individuals with SIB also noted that up to 90% suffered from severe-to-profound ID (Griffin et al. 1986). The same relationship between lower IQ and a motor stereotypies factor score is found in a sample of 316 children and adults with autism (ages 20 months to 29 years) (Lam et al. 2008). When individuals with autism and non-autism ID are considered, stereotypies are predicted by having autism + lower nonverbal IQ, compared to not having autism (Goldman et al. 2009; Bradley et al. 2011). The sum of the data supports a relationship between lower adaptive functioning (a proxy for lower IQ) and increased RBs.

The preponderance of RBs within our cohort may also be linked to the high prevalence of autism features associated with CdLS. Autism or autistic features are present in 47–62% of individuals with CdLS (Moss et al. 2008; Oliver et al. 2008). Our cohort did not undergo formal evaluation for a diagnosis of autism; however, 88% (n = 44) of the participants had a Childhood Autism Rating Scale (CARS) total score ≥ 30 (data not reported in the present study), raising concern for a diagnosis of autism based on this cutoff (Chlebowski et al. 2010). However, within our sample, socialization was a relative strength compared to other domains of adaptive functioning, suggesting an atypical autism profile, as noted previously (Srivastava et al. 2014). In light of this atypical autism profile, it might be appropriate to say that children with CdLS have autistic *traits*, in particular communication deficits and a preponderance of RBs. The preponderance of RBs also raises the possibility of obsessive compulsive disorder (OCD). Again, the children in this cohort did not undergo formal evaluation of OCD. Regardless, providing such a diagnosis can be difficult in light

of the overall degree of adaptive impairment seen in this cohort—likely reflecting overall degree of ID. While RBs could be seen as a form of compulsions, based on the degree of adaptive impairment in our patients, it is difficult to establish whether these behaviors are designed to alleviate some sort of stress or urge, in accordance with Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5) criteria (American Psychiatric Association 2013). Nonetheless, the overlapping presentations of these comorbidities are intriguing and deserve further investigation in CdLS.

The current data do not show a significant association of age with SIB, within the pediatric age range. This finding contrasts with a study of 49 individuals with CdLS, in which self-injury occurred in 82% of those over 12 years of age and 42% of those under 12 years of age (Berney et al. 1999). Notably, this prior study included adolescents/adults for 1/3 of the sample. In other developmental disorders, abnormal sensory processing and need for sameness, but not older age, are associated with an increase in SIB (Duerden et al. 2012).

Surprisingly, our data did not show a significant association between health status (such as presence of GERD) and SIB. GERD is a common complication of CdLS and can serve as a precipitant for SIB (Luzzani et al. 2003). This study was not designed to characterize symptoms of GERD in relation to behavioral abnormalities which may be the explanation for the non-association of GERD with SIB seen in our cohort. Specifically, severity and frequency of GERD symptoms, as well as time course of GI symptoms, was not obtained, possibly diminishing the association. The same rationale may apply to why other health metrics (such as history of diaphragmatic hernia, malrotation/volvulus, other severe GI malformation) did not correlate with SIB: the study did not characterize severity of these symptoms or whether they were impairing during the time period of assessment of behavioral symptoms.

The relationship between genetics pathways involving *NIPBL* and the clinical phenomena of RBs and SIB is yet to be elucidated. Molecularly, *NIPBL* impacts cohesin formation, and it acts as a developmental regulator for multiple other organ systems, including the brain (Kawauchi et al. 2016). Anatomically, a report on structural MRI findings in 15 individuals with CdLS notes that two-thirds have some degree of cerebral atrophy, white matter changes, cerebellar hypoplasia, and/or enlarged ventricles (Roshan Lal et al. 2016), which is consonant with prior autopsy findings in patients with CdLS, which noted central nervous system (CNS) hypoplasia and fewer cerebral convolutions (Vuilleumier et al. 2002; Yamaguchi and Ishitobi 1999). Given that RBs are generally associated with decreased frontal and executive functioning, along with the execution of programmed motor sequences of subcortical origin, or "loss of control of habitual behaviors" (Burguière et al. 2015), future studies of CdLS need to examine the impact of CdLS-related gene disruptions on brain structure and function, along with the downstream dysfunctional behavioral consequences, such as RBs and SIB.

Limitations

The current study has several limitations. First, the RBs described are not necessarily specific to CdLS. Rather, they may reflect behavioral features seen in ID generally, thus a comparison group is needed to argue for specificity for particular RBs in CdLS. In addition, it is not known whether the frequencies of RBs are different than controls, which when unaffected with psychiatric disorders, are not straightforward to identify. Second, there may be a referral bias. The individuals included in this behavioral study were self-referred by their families and caregivers, which may make the sample lean towards a more severely behaviorally impaired cohort, limiting generalizability to all children with CdLS. Third, further generalizability is limited by the fact that the genotypes of the participants are largely unknown, and hence genotype–phenotype correlations cannot be applied to the general population of individuals with CdLS. For example, not only do individuals with some *SMC1A* variants have milder systemic and behavioral presentations compared to individuals with *NIPBL* variants, but they may also have in some cases a different neurobehavioral profile (i.e., Rett syndrome-like including epileptic encephalopathy, stereotyped movements, and regression) (Huisman et al. 2017). As a result, the likely genetic heterogeneity of this cohort may skew impressions of the behavioral profile observed. Fourth, we applied older (2007) diagnostic criteria to ascertain a clinical diagnosis of CdLS (Kline et al. 2007). Updated (2018) diagnostic criteria exist (Kline et al. 2018), so it is possible some individuals in this cohort may not actually have CdLS. However, this possibility is mitigated by the fact that all participant diagnoses were reviewed by a clinical expert in CdLS (ADK). Fifth, while impaired adaptive functioning is a reasonable proxy for ID, it does not replace standardized psychological testing to assess cognitive capacity, and such testing was not performed uniformly in this study. Limitations aside, the work presented here builds our understanding of RBs in children with CdLS including compulsions, stereotypies, and SIB. The behavioral phenotype of CdLS may be germane to the study of stereotypies and SIB in general, specifically pathophysiology and treatment.

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Author contribution SS, MG, ADK made substantial contributions to the conception or design of the work; BC, CL-S, EO and SW contributed to the acquisition, analysis, and interpretation of data for the work.

All authors contributed to drafting the work or revising it critically for important intellectual content as well as approved the final version.

Compliance with Ethical Standards

Conflict of interest Dr. Wilkinson has received contract funding administered through Yale University from Janssen and Sage Therapeutics for the conduct of clinical trials; he anticipates receiving contract funding from Oui Therapeutics and LivaNova. He has received consulting fees from Janssen, Oui Therapeutics, and Biohaven. Dr. Srivastava has received consulting fees from Guidepoint. The other authors have no other conflict of interest to disclose.

Ethical Approval This was research with human participants, and all participants provided informed consent. Research was approved by the IRB at Johns Hopkins University School of Medicine. We appreciate the help from families and staff of the CdLS Foundation.

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