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Behavioral and Psychiatric Manifestations in Cornelia de Lange Syndrome (CdLS)

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Abstract

Purpose of review: Cornelia de Lange Syndrome (CdLS) is a rare genetic syndrome with clinical manifestations due to multiple affected organ systems including limbs, gastrointestinal, skin, central nervous systems. While the genetic basis of CdLS is now uncovered, how behavioral manifestations are associated with genetic and brain differences are less well understood. The current focused review systematically describes the main behavioral observations to date in individuals with CdLS, which have a significant impact on quality of life and adaptive functioning.

Recent findings: The CdLS behavioral phenotype includes autistic traits as a prominent feature; however, brain imaging studies, required to understand gene-brain-behavior connections in CdLS, are scarce. Moreover, autistic features in CdLS have a greater emphasis on repetitive behaviors, including self-injurious behaviors (SIB), and expressive communication deficits, different that the core social deficit seen in idiopathic autism. Current data strongly support the use of CdLS as a model disease for repetitive behaviors and associated developmental delay manifestations.

Summary: Behavioral phenotype characteristics in CdLS point to a preponderance of repetitive clinical phenomena as well as expressive verbal deficits which ought to inform specific treatment approaches in CdLS. In particular, repetitive behaviors associated with self-injury are of high negative impact on the quality of life for individuals with CdLS and their families. Treatment approaches geared to manage repetitive behaviors and SIB in CdLS are required in this developmental condition.

Keywords

repetitive behaviors; anxiety; sleep problems; self-injury

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Introduction

Cornelia de Lange syndrome (CdLS) is a genetic disorder characterized by developmental abnormalities in multiple organ systems, including brain, bone, gastrointestinal, immune, endocrine and others [1]. The somatic phenotype includes abnormalities of the upper limbs, gastroesophageal dysfunction, cardiac, ophthalmologic and genitourinary anomalies, hirsutism [2]. Historically, CdLS was named when Cornelia de Lange, a Dutch pediatrician, described 2 patients with characteristic facial features include long eyelashes, confluent eyebrows (synophrys), long philtrum, thin lips and crescent-shaped mouths in 1933 [3]. The behavioral phenotype was early noted for characteristic self-injurious behaviors including self-biting, skin picking and [4], as well as repetitive behaviors including “circling, twirling and whirling” and hand posturing [5]. At the time, Nyhan observed that children with CdLS appeared to be “[have] self-programmed…stereotyped patterns of unusual behavior [which] could represent the presence of structural defects in the central nervous system, just as there are structural defects in the hair, the bones, and the dermatoglyphics” [5].

Contemporary research has demonstrated that CdLS is caused by mutations in genes that support the development and function of the cohesin complex, a protein network which regulates the separation of sister chromatids during cell division in mitosis or meiosis [6]. To date over 300 potentially causal mutations have been identified in cohesin-related genes, including the main cohesin gene *NIPBL*, as well as *SMC1A*, *SMC3*, *RAD21*, and *HDAC8* [7]. While CDLS causal genes have critical roles in cohesin formation, they also have been shown to have regulatory roles in organ development, which are still being uncovered [8]. In developmental animal research, the analogue of *NIPBL*, *nipped-b*, has been studied in Drosophila models, demonstrating a role for *nipped-b* in fruitfly growth, learning, memory, and circadian rhythms [9]. The wide ranging effect of *nipped-b* mutations may respond to its role in promoting enhancer-promoter communication in gene developmental systems [10], which in turn can widely impact developmental systems in humans.

The impact of *NIPBL* and other CdLS-causal mutations on brain neurocircuitry is still yet to be elucidated. Anatomical autopsy reports suggest significant brain insults secondary to CdLS causing gene mutations including hypoplasia of the anterior thalamic nuclei, neurohypophysis, lateral geniculate body, cerebral peduncle, ventral pons and cerebellar internal granular layer, as well as heterotopic cell nests in the cerebellar white matter and immature or simple convolution pattern of the cerebral gyri [11]. This latter characteristic is reminiscent of lissencephaly, a condition with underdeveloped cerebral gyri due to mutations in another developmental gene, *Gli3* [12**]. It should be noted that Gli3, a zing finger transcription factor, belongs to a genetic network which determines limb formation, another important clinical feature in CdLS [13, 14], setting the groundwork for investigations into the developmental connections between limb and brain development, as observed in CdLS [15]. Another autopsy study reported abnormal convolution patterns of the cerebral gyri and frontal lobe hypoplasia [16]. More recent studies of brain imaging scans used for clinical purposes reveal dysplastic changes in brain structure such as cerebral atrophy, white matter changes, cerebellar hypoplasia, and enlarged ventricles [17].

Supporting Nyhan's observation of 1972, the extensive brain structure differences in individuals with CdLS point to an array of maladaptive behaviors observed in children and adults with CdLS. In this chapter, a focused review of subsets of behavioral differences which describe a behavioral phenotype in CdLS will be presented. For this purpose, the categories of behavioral differences will include general developmental/intellectual delay, speech difficulties, social deficits, repetitive behaviors and sleep problems subsections.

Phenomenology

A. Intellectual Disability and Developmental Delay

Intellectual disability (ID) is a hallmark of CdLS, with most individuals having IQ of moderate intellectual disability with IQs in the range of 55–70 [18]. Earlier reports of the phenotype established that ID occurred in up to 100% of individuals with CdLS [19], however, a milder phenotype with less affected general intelligence scores are now widely described in the literature. The general notion that deletions which affect the cohesin genomic product to a larger extent, such as those affecting multiple exons, correlate with a more severe physical and intellectual phenotype has held true in most studies. For example, in one individual with a deletion of only exon 11, resulting in an in-frame deletion of the *NIPBL* gene, the intellectual phenotype was only mildly affected [20]. In the same manner, more severed forms of ID in CdLS predispose to a greater array of maladaptive behaviors [21], with several studies finding that autistic traits [22] and disruptive behaviors are highly correlated with the level of adaptive functioning [23,24]. Finally, the severity of ID status has been found to correlated with the type of cohesin-gene mutation [25], but no mutation type has been found to be associated with specific type of maladaptive behaviors [24]. In a study focusing on predictors of more severe ID in CdLS, the number of malformations, and the presence of limb deficits were the only predictors positively linked to more severe ID. Although cleft lip/palate was also associated with ID in CdLS [26], this somatic characteristic is not as typical of CdLS as limb deficits.

B. Speech Difficulties

Expressive language difficulties are common in individuals with developmental disabilities and in particular in specific genetic syndromes. Individuals with Williams syndrome, caused by a deletion of the chromosomal region 7q11.23 affecting multiple genes, display hypersociability with hyperverbal concrete language states alongside a notable weakness with visuospatial construction [27]. In contrast, in trisomy 21 (Down syndrome) one can also find a clinical presentation with no social deficits alongside a striking deficit in expressive language skills [28]. Early clinical observations resulted in numerous reports of low verbal output or even absence of speech in individuals with CdLS, mostly based on case reports [29]. In a larger study of 116 individuals with CdLS 2 months to 29 years of age, Goodban et al. [30] reported a lower ability to express than comprehend language, a lack of syntactic ability despite vocabulary skills, and a notable tendency to not use language expressively despite some ability present. Errors in articulation were common and consonants distorted or missing in the diction. Severe language delay was predicted by low birth weight, hearing impairment, upper limb malformations, social deficits and severe motor delays [30]. Another study used survey methodology to report on 27 children with

CdLS, of which only 4 were able to use speech, while most of the older children used nonverbal means to communicate needs [31]. Early language therapeutic interventions are thus indicated, and can produce favorable outcomes in higher-functioning individuals with CdLS [32]. Therapy might be aiding the strengthening of vocalization musculature, which is surmised to be abnormal in CdlS, as the glottal 'fry' (a nonperiodical phonation of the vocal folds in a frequency below the normal pitch register) has been observed in younger children with CdLS, along with hoarseness in older individuals with CdLS [33].

C. Autism Spectrum Disorder

Social deficits constitute the core autistic trait in idiopathic autism, either due to widespread developmental brain insults or more specific social brain network abnormalities [34]. Clinical observation and research data, however, point to genetic syndromes displaying mostly atypical autism syndromes. In Fragile X, for example, examination of brain structure in idiopathic autism and individuals with Fragile X show notable differences in caudate and amygdala volumes between the two groups [35]. Concurrent with reports of atypical autism features in other genetic syndromes, a study of 41 children with CdLS (23 females and 18 males) ages 5–18 years, used the Childhood Autism Rating Scale (CARS), classifying 17% as having no autism, 41 % mild autism and another 41% as severe autism. The clinical profile consisted of absent or poor expressive language, along with rigid, stereotypical movements and behaviors. Social deficits were relatively less prominent features, although remained a clinical concern [22]. An additional report on 49 individual with mild to severe phenotypic CdLS also found a 49% prevalence of significant autistic features using the Social Communication Questionnaire (SCQ), and the Autism Diagnostic Interview-Revised (ADI-R). In both studies, as expected, a higher number of autistic features correlated with lower adaptive and intellectual functioning [36]. An earlier study also using the CARS, identified 32% of 54 individuals with CdLS as having autism, compared to 7% of an ID comparison group [21], suggesting that autistic features are common in CdLS, often in conjunction with lower adaptive function [37]. Supporting the common occurrence of ASD traits in CdLS, a longitudinal study of a large number of patients with Fragile X syndrome, Cri du Chat and CdLS were followed for autism domain symptoms. While patients with FXS and CdLS had higher number of autism features at Time 1, at the Time 2 30-month follow-up visit patients with CdLS had the most autism-related clinical features [38]

D. Repetitive and Self-Injurious Behaviors

The presence of repetitive and compulsive behaviors (RCBs) and self-injurious behaviors (SIB) in individuals with CdLS has been one of the most consistent behavioral expressions in clinical reports. Compulsive behaviors, which denote behaviors which are ego-dystonic or displeasing, but which the patient feels compelled to perform, include SIB. Behavioral phenotypes of SIB include the Lesch-Nyhan syndrome (LNS), in which patients engage in repetitive self-injury in a compulsive fashion [39]. In clinical reports of CdLS, repetitive behaviors are universally present, while frank SIB is reported in approximately 40% of cases [31,40]. Earlier reports associated SIB in CdLS with somatic complaints, including gastro-esophageal reflux disorder (GERD) [41], a common medical condition in CdLS [42]. However, due to the awareness of this complication in individuals with CdLS, this condition is now more widely treated and less associated with SIB. More recently, the association of

SIB with the frequency of non-SIB RCBs, such as stereotypies and ritualistic tendencies has been noted [40,43,44], supporting a prior study which found that 60% of 56 patients with CdLS display SIB, which correlated highly with the presence of self-restraint maneuvers as well as a range of compulsive behaviors [45]. It is notable, that several reports associate older age with worsening adaptive function and SIB [23] in a subset of individuals with CdLS, possibly pointing to abnormal aging in CdLS, a clinical phenomenon largely understudied to date [46]. In a study of 27 patients with CdLS and SIB, compared to 17 patients with CdLS and no SIB, there was no difference in the degree or number of environmental cues that may have been related to SIB [47]. Thus, the experience of self-restraint in the setting of SIB for patients with CdLS, points to an endogenous cause for the SIB, in distinction with other forms of SIB which may be largely responsive to environmental cues.

E. Anxiety

Clinical reports of individuals with CdLS have noted a high degree of anxiety in a subset of children and adults. Anxiety often takes the form of social avoidance as well as mounting anxiety when routines or ritualistic behaviors are not completed. Socially avoidant behaviors can take the form of reduced verbal interaction or even selective mutism. In an observational study of 12 children with CdLS, social anxiety was noted in children with CdLS by displayed patterns of eye contact and speaking, in the context of social demands [48]. Additional research exploring social anxiety and other forms of anxiety in CdLS are needed to better understand the behaviorally inhibited stance in this group of children and adults with CdLS.

F. Hyperactivity

Clinical observations of hyperactivity have been prevalent in reports of behaviors of children with CdLS [49]. Often the manifest behavior is of motoric hyperactivity, possibly reflecting a need for vestibular stimulation, as well as the presence of GERD [41]. Of note, hyperactivity in one study was associated with an elevated level of SIB [43].

E. Sleep Problems

Sleep difficulties are prevalent in CDLS, with over half of individuals reportedly suffering from sleep problems in clinical surveys [23, 50]. In a study of 46 individuals with CdLS the Sleep Disturbance Scale for Children (SDSC) was administered. Of this sample, up to 15% showed an abnormal total sleep score, with another 56% showing borderline abnormal scores. A higher proportion of sleep symptoms were associated with epilepsy, gastro-esophageal reflux disorder (GERD), ID and maladaptive behaviors. There was no association with CdLS causal genes and sleep severity scores [51]. Other studies support sleep abnormalities, both in adults and children with CdLS. Rajan et al. [52] report on 31 individuals with CdLS, including 19 children. Children with CdLS have the worst sleep patterns, with 50–75% of children having circadian rhythm disorders, compared to 33% of adults with CdLS, rates much higher than those reported in the general population. Children also take longer to fall back to sleep and have more nighttime awakenings [52]. Sleep disordered breathing (SDB) has also been identified in children with CdLS, using the Pediatric Sleep Questionnaire (PSQ) and the Pediatric Daytime Sleepiness Scale (PDSS). Of

22 patients, up to one-third were found to have moderate to severe SDB, while in the population estimates of SDB are approximately 1–4%. Daytime sleepiness using the OSA18 questionnaire was also seen in about one-quarter of patients [53]. Finally, Hall et al [50] used a control sample of mixed intellectual disability patients to assess medical conditions including sleep problems, which were not found to be related to self-injurious behaviors.

Conclusions

CdLS is characterized by a behavioral phenotype displaying a preponderance of repetitive clinical phenomena, as well as expressive verbal deficits. Social deficits, although present, are less prominent. These behavioral features can be used to inform specific treatment approaches in individuals with CdLS. In particular, repetitive behaviors associated with self-injury are of high negative impact on the quality of life for individuals with CdLS and their families, and should be specifically targeted for intervention.

Abbreviations:

CDLS	Cornelia de Lange syndrome

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• of special interest

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Key points:

- Individuals with CdLS have autistic features characterized by repetitive behaviors, self-injurious behaviors, and deficits in communicative abilities, with less impact on social deficits.
- Common associated behavioral manifestations in individuals with CdLS include hyperactivity, anxiety symptoms, and sleep problems.
- Older individuals with CdLS may manifest rapidly increasing adaptive deficits with concomitant neuropsychiatric symptoms.