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Improvement in hearing loss over time in Cornelia de Lange syndrome

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ABSTRACT

Objectives: Patients with Cornelia de Lange Syndrome (CdLS) are reported to have conductive (CHL) and sensorineural hearing loss (SNHL), but there is little information pertaining to the progression of hearing loss over time. The goal of this study was to examine the prevalence of CHL and SNHL in adults and children with CdLS and look for changes in SNHL over time.
Methods: Retrospective chart review of patients with CdLS presenting to a CdLS clinic was conducted. Also, a written survey of clinical concerns was collected from additional patients/families seen in the clinic and through the Cornelia de Lange Foundation.
Results: Seventy-eight patients (50% female) were included in the chart review. Mean age was 16.8 ± 11.4 years (range-0.6–50 years) and mean age at diagnosis of hearing loss was 4.6 ± 10.6 years (n = 26). Five patients (6.4%) had severe to profound SNHL that improved with time, including 2 who had complete normalization of audiogram results. Thirty-five families/patients completed the clinical survey, and 45.5% of the families reported a noticeable improvement of hearing over time.
Conclusions: Conductive hearing loss and SNHL are common in CdLS. More than 50% of the patients seen in an adult CdLS clinic reported improvement in hearing loss over time, and a subset of patients had an improvement in SNHL. In light of these findings, we recommend longitudinal evaluations of hearing loss in these patients with both auditory brainstem response and otoacoustic emissions testing if SNHL is identified.

1. Introduction

Cornelia de Lange syndrome (CdLS) is a rare developmental disorder with variable expression affecting multiple organ systems and intellectual function [1]. With an estimated incidence of 1:10,000 to 1:46,000, CdLS frequently presents with growth restriction along with craniofacial, musculoskeletal, cardiac, neurological, and digestive tract abnormalities [2,3]; manifestations of the syndrome can range from mild to severe. The craniofacial anomalies of children affected by CdLS are useful for clinical diagnoses and include microcephaly, synophrys, long thick eyelashes, low-set ears, a depressed or broad nasal bridge, smooth philtrum, high arched or cleft palate, small widely-spaced teeth, and a short neck [4,5]. CdLS is routinely diagnosed in the first year of life, although milder cases may go unrecognized for years [3]. This syndrome has been linked to mutations encoding genes related to the cohesin complex, especially the Nipped-B-like (NIPBL) gene with a prevalence of 60% [6,7], structural maintenance of chromosomes (SMC) 1A gene with a prevalence of 5% [7,8], and less frequently SMC3, RAD21 cohesin complex component and histone deacetylase (HDAC) 8 which combined constitute 5% of all cases [8–10]. Most of these are thought to be sporadic. The

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presence of NIPBL mutations carry the greatest risk for the severe (classical) phenotype, whereas the other mutations may manifest as mild to moderate [11,12].

Both conductive hearing loss (CHL) and sensorineural hearing loss (SNHL) have also been reported in children with CdLS, the former in part due to external auditory canal stenosis (30%) and serous otitis media (SOM) (50%) [13]. Sataloff et al. [13] published a study of 45 patients with CdLS and reported that SNHL was present in 85%; mild (21–40 dB) loss was seen in 24%, moderate (41–65 dB) was seen in 24%, and severe loss (65–90 dB) was seen in 52%. Marchisio et al. [14] found in 2014 that the increased prevalence of severe SNHL in patients with CdLS is likely caused by truncation of the NIPBL gene.

In light of the fact that severe hearing loss has been associated with poor language development, treatment for hearing loss has focused on early identification and appropriate intervention, ideally initiated prior to the typical time for language development [1]. Further, intellectual disability frequently seen in patients with CdLS makes the reliability of hearing thresholds in younger children more unreliable and inconsistent. However, no published data exist that evaluates the course of hearing loss over time in children and adults with CdLS. The primary goal of this study was to look at hearing status over time in patients with CdLS, as well as to examine clinical features associated with hearing loss.

2. Methods

2.1. Clinical evaluation

This is a retrospective case series of all patients with a diagnosis of CdLS who were seen at a CdLS specialty clinic at the Greater Baltimore Medical Center (GBMC), or in the pediatric otolaryngology clinic at the Johns Hopkins School of Medicine were included, between April 2006 and June 2012. Demographic data included age, sex, diagnosis, audiological studies, temporal bone imaging records, comorbid illnesses, and treatments. Severity of hearing loss was defined as mild (21–40 dB), moderate (41–65 dB), severe (65–90 dB), and profound (>90 dB).

2.2. Survey

A separate group of patients with CdLS was prospectively recruited to participate in a data collection survey. Surveys were distributed at the CdLS specialty clinic in 2011 and 2012 and at the annual meeting of the CdLS Foundation in 2012. Advertisements were distributed in the CdLS Foundation Newsletter in 2011 and 2012. Questions pertaining to hearing loss included previous hearing evaluations, history of known hearing loss, presence and frequency of ear infections, and ear tube placement. Surveys were filled out by the caregivers, or by the patients themselves.

3. IRB

The chart review and the survey were approved by the institutional review boards (IRBs) from both the Johns Hopkins Hospital and GBMC; the CdLS Foundation also approved this work. All data was handled per IRB guidelines in order to protect patient privacy.

3.1. Data analysis

Descriptive statistics was performed, yielding the mean, median, mode and standard deviations, which were calculated using Stata 12 (Stata Corporation, College Station, TX).

4. Results

Medical records of 78 patients were reviewed, 39 (50.0%) of whom were female. The mean age was 16.8 ± 11.4 years and ranged from 7 months to 50 years. Forty one (52.6%) patients were under the age of 18. Age at the time of hearing loss diagnosis was available for 32 patients with a mean age of 4.1 ± 10.0 years. Fifty nine (75.6%) of the patients had level of disability listed in the medical records, and most (55%) had severe cognitive impairment (described as mild, moderate and severe in the charts). Additional demographic information is summarized in Table 1.

Forty (51.2%) patients were diagnosed with hearing loss prior to their evaluation in the clinic. Of the remaining 38 patients, 5 (6.4%) patients had normal hearing based on a complete audiogram available for review, 4 (5.1%) had presumed hearing loss without conclusive hearing evaluation and only a diagnosis listed in the chart, and 28 (35.9%) had no mention of hearing loss as a diagnosis in the chart or any hearing evaluation for review. The type of hearing loss at the time of diagnosis was identified by chart review in 31 patients: 22 (71%) had SNHL, 6 (19%) had CHL, and 3 (10%) had mixed hearing loss. Of the 78 patients included for chart review, the type of hearing evaluation was listed in medical records for 51 patients (65.4%). Thirty-one patients (39.7%) had complete audiograms, 2 (2.6%) had behavioral testing, 8 (10.3%) had ABRs, and 10 (12.8%) had optoacoustic emissions. The remaining 27 patients did not have the type of hearing evaluation listed in the medical records.

Five (16%) of the patients who were definitively diagnosed with hearing loss described significant improvements in hearing over time, with 2 of the 5 subsequently found to have normal hearing on audiologic evaluation at follow-up. A typical example is that of a 23 year old with a diagnosis of severe SNHL from a complete audiogram as a young child who was found to have normal hearing during a follow-up visit. A second patient was diagnosed with profound hearing loss as an infant and wore hearing aids until the age of 4.4 years. His audiogram at 6 years of age demonstrated only mild hearing loss of 35 dB. A third patient had mixed hearing loss which was improved at time of clinic visit at the age of 22. One patient was diagnosed with bilateral hearing loss and was dispensed hearing aids. Documentation demonstrated improved hearing in the right ear based on a complete audiogram in this

Table 1
Demographic characteristics of patients seen in the CdLS Clinic who provided ear and hearing history.

Category	Number (N=)	Percentage (%)
Age (years)		
0–10	25	32.1
10–20	20	25.6
20–30	22	28.2
30–40	8	10.3
40–50	0	0.0
50+	1	1.3
Unknown	2	2.6
Race		
Caucasian	51	65.4
African American	7	9.0
Hispanic (non-white)	4	5.1
Mixed	6	7.7
Unknown	8	10.3
Gender		
Male	39	50.0
Female	39	50.0
Cognitive impairment		
Mild	16	27.1
Moderate	10	16.9
Severe	33	55.9