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Cornelia de Lange Manifestations in Otolaryngology: A Systematic Review and Meta-Analysis

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Objectives: Cornelia de Lange syndrome (CdLS) is a rare genetic disorder. Our goal was to systematically review the literature regarding otolaryngology manifestations of CdLS.

Methods: We systematically reviewed the PubMed, Embase, CINAHL, Scopus, and Google Scholar databases for original articles of otolaryngology manifestations for patients with CdLS. These articles were analyzed, and pooled prevalence was calculated.

Results: We analyzed 1,310 patients included in 35 case series and 34 case reports. Hearing loss was present for many patients (27 studies), with sensorineural hearing loss affecting 40.3% (95% confidence interval [CI]: 17.3–63.4) and conductive affecting 22.7% (95% CI: 5.7–39.7). Recurrent acute otitis media was the most frequent infectious manifestation, with 56.5% (95% CI: 34.1–78.4) in seven studies, followed by recurrent airway infections with 44.1% (95% CI: 11.0–87.1) in five studies. Forty-nine (49.7%) percent of patients (95% CI: 25.9–73.6) in nine studies had dysphagia, and 76.6% (95% CI: 59.8–93.3) in four studies had some degree of dysphonia. Craniofacial anomalies were reported in 30 studies, with micrognathia (53.1%; 95% CI: 34.1–72.1) and high arched palate (70.6%; 95% CI: 56.5–84.8) commonly reported. Additional physical exam abnormalities reported included those involving: lips (76.8%; 95% CI: 65.3–88.4), dentition (65.1%; 95% CI: 27.2–100), mouth (85.5%; 95% CI: 76.2–93.8), and eyelashes (87.1%; 95% CI: 77.2–96.9). Sleep-disordered breathing or obstructive sleep apnea affected 25.8% (95% CI: 11.4–40.2) of patients (7 studies). Airway anomalies were reported in 11 case reports.

Conclusion: This is the first comprehensive evaluation of otolaryngologic manifestations in the CdLS literature. Most reported hearing loss and craniofacial anomalies. Sleep disorders occurred in a minority of patients, whereas airway disorders were primarily reported in case reports. These conditions should be further examined given their potential life-threatening implications.

Key Words: Cornelia de Lange, CdLS, otolaryngology, ENT, syndrome, genetic disorder, NIPBL, hearing loss, sleep, dysphagia, dysphonia, craniofacial anomalies.

Level of Evidence: 3a

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INTRODUCTION

Cornelia de Lange syndrome (CdLS) is a rare genetic disorder characterized by distinctive craniofacial features, limb abnormalities, and intellectual disability with an estimated prevalence between 1.6 to 2.2 per 100 thousand.[1,2] Diagnosis is typically based on clinical assessment and then confirmed with genetic testing (NIPBL, SMC3, SMC1A).[3] This disorder can present with clinical features affecting many different organ systems, including cardiovascular, gastrointestinal, musculoskeletal, craniofacial, and neuropsychiatric manifestations with variable penetrance. Gastroesophageal reflux disease (GERD) is one of the most commonly seen comorbidities resulting in significant feeding difficulties.[4] In addition, cardiac septal defects and the absence of the forearms and digits are also frequently reported.[2]

Specific craniofacial features in these patients are characteristic and common manifestations. Most patients have synophrys; long, thick eyelashes; small anteverted nares; micrognathia; and cleft or high-arched palate.[5] Hearing loss is also extremely common in these patients due to external, middle, and inner ear anomalies.[6] Although these manifestations are among the most common ones reported, limited information is published regarding the prevalence of each. Due to the complexity of this disorder, the first international consensus statement was recently published.[6] However, due to the breadth of included recommendations, it provides only a limited review of otolaryngology manifestations and is not designed to be a comprehensive, systematic review of the literature.

Aside from hearing loss, a wide variety of otolaryngologic disorders have been reported, including airway problems, dental and oral cavity anomalies, and sleep disorders, although these disorders are less frequently described. Careful study and accurate description of all otolaryngology-related features are important to

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appropriately care for these patients and counsel families. In particular, knowledge of the prevalence and severity of these manifestations is important to prevent future complications and ensure appropriate management of these patients.

The goal of this study was to systematically review the literature regarding otolaryngologic manifestations in patients with CdLS. We highlight the following areas of interest: otologic, infectious, sleep, voice and airway, gastrointestinal, oral cavity and dental, as well as craniofacial manifestations.

METHODS

The study methodology was based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist and statement recommendations.[7] The following inclusion criteria were used for this study: 1) subjects of all ages, 2) mention of otolaryngology manifestations, 3) contained an abstract, 4) either English or French-language studies, 5) included a minimum of one human patient, and 6) were not classified as review articles or meta-analyses. We excluded those publications in which only the abstract was available, unpublished manuscripts, and letters to the editor. Case reports were considered in a separate category to ensure that all possible manifestations were identified.

A computerized search was conducted by two medical librarians to identify literature articles. The comprehensive literature search was performed using PubMed, CINAHL, Scopus, Embase, and Google Scholar database as of March 30, 2018. Search terms used included the following keywords: "Cornelia de Lange syndrome," "de Lange syndrome," "otolaryngology," "ENT," "ears or sinus or mouth or palate or voice or hearing or otitis or hearing loss or facial," "sleep disorder," "obstructive sleep apnea or snoring or sleep disordered breathing." The reference sections of identified studies were also searched to identify additional articles for review. The search strategy was created in conjunction with these medical librarians using Medical Subject Headings intended for PubMed and then tailored for the other databases (Table I). Two or more independent investigators reviewed all identified titles, abstracts, and full-text articles to determine if they met inclusion criteria (Fig. 1). Duplicates articles were removed. Any disagreement regarding inclusion was resolved with a discussion between the two reviewers, and consensus was obtained.

The remaining articles were then reviewed, and those that did not meet inclusion criteria were excluded. A final review of included articles was then performed by the entire research group. Each article was then categorized by the type of abnormality reported: ear anomalies; hearing loss; sinus disease; voice disorder; ear, nose, and throat infections; GERD; craniofacial anomalies; and sleep and airway disorders. Case reports are presented separately.

The quality of included articles was also reviewed by at least two reviewers. The level of evidence was determined according to the Center for Evidence-Based Medicine guidelines.[8] Due to the nature of this systematic review, no Institutional Review Board was required by our institution. Furthermore, the quality of the studies was evaluated using the Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses.[9]

TABLE I.
MeSH Terms Used for Comprehensive Literature Search on the Topic of Otolaryngology Manifestations for Patients With Cornelia de Lange Syndrome.

Database	MeSH Term
PubMed	((Otolaryngology OR ears OR sinus OR nasal OR mouth OR palate OR voice OR hearing OR ear OR otitis)) AND ("Cornelia de lange syndrome" OR "de lange syndrome" OR "de lange syndrome"[MeSH Terms])
	(((obstructive sleep apnea or snoring or sleep disordered breathing)) AND ("Cornelia de lange syndrome" OR "de lange syndrome" OR "de lange syndrome"[MeSH Terms])) AND english[language]
	AND english, french [language]
CINAHL	(MH "Otorhinolaryngologic Diseases+") OR "Otolaryngology" OR (MH "Ear+") OR (MH "Ear Diseases+") OR (MH "Paranasal Sinuses+") OR (MH "Nose+") OR "nasal" OR (MH "Nose Diseases+") OR (MH "Mouth+") OR (MH "Mouth Diseases+") OR (MH "Palate+") OR (MH "Voice+") OR (MH "Voice Disorders+") OR (MH "Hearing+") OR (MH "Hearing Disorders+") OR (MH "Otitis+") OR Otolaryngology OR ears OR sinus OR nasal OR mouth OR palate OR voice OR hearing OR ear OR otitis, MH "Sleep Apnea, Obstructive") OR sleep disordered breathing OR (MH "Sleep Disorders+") OR (MH "Snoring") OR snoring OR obstructive sleep apnea
Scopus	(TITLE-ABS-KEY (de AND lange AND syndrome) AND TITLE-ABS-KEY (otolaryngology OR ears OR sinus OR nasal OR mouth OR palate OR voice OR hearing OR ear OR otitis)) AND (LIMIT-TO (LANGUAGE, "English", "French") (obstructive AND sleep AND apnea OR snoring OR sleep AND disordered AND breathing)
Embase	'de lange syndrome'/exp AND (('sleep disordered breathing'/exp OR obstructive) AND sleep AND apnea OR 'snoring'/exp)
Google Scholar	ENT or otolaryngology manifestations in Cornelia de Lange, sleep disorders in Cornelia de Lange

ENT = ear, nose, and throat; MeSH = medical subject headings.

The outcomes were treated as a proportion of prevalent variables and reported with 95% confidence intervals (CI). Statistical heterogeneity was assessed with the I^2 statistic, and significance was assumed when the I^2 was greater than 50%. Because of the clear differences among the included studies and several uncontrolled variables, we used a random-effect model to perform a proportional meta-analysis of case series studies. The software used to plot the studies in the meta-analysis was Comprehensive Meta-Analysis software V3 (Biostat, Englewood, NJ).

RESULTS

Three-hundred and fourteen English-language articles were identified. After final review, 69 studies were selected for inclusion: 35 case series and 34 case reports. All 35 case series were level 4 evidence with a combined number of participants of 1,276. The results of the case series are presented below and in Tables II–IV, Figures 2–4, and Appendices 1 through 3. Furthermore, case reports (n = 34) were analyzed separately to ensure that we also

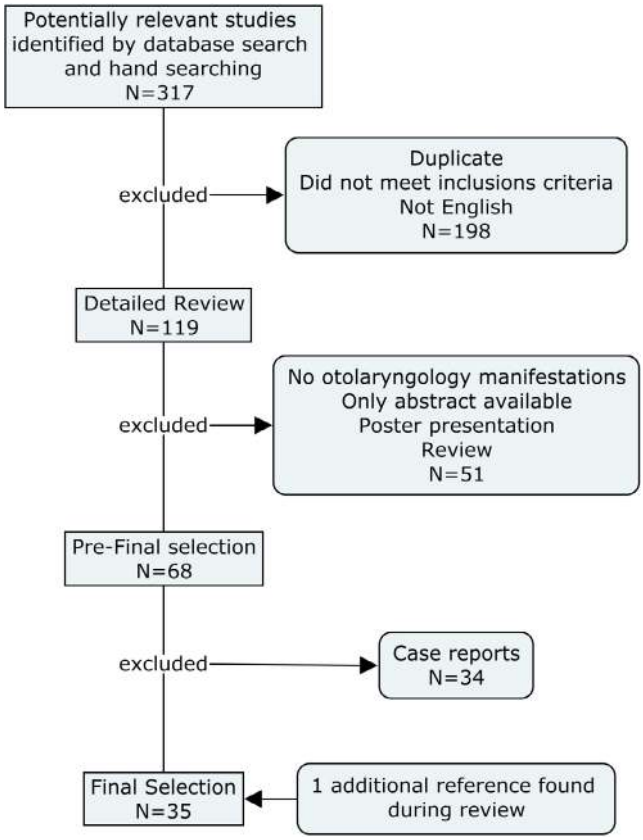

Fig. 1. Flow diagram of a literature search for manuscripts dealing with otolaryngology manifestations of Cornelia de Lange syndrome.

covered underreported or life-threatening manifestations of CdLS. Case reports are detailed below and in Table III.

Otologic Manifestations

Twenty-five case series reported on otologic manifestations of CdLS (Table II). Hearing loss was reported for many of these patients, with sensorineural hearing loss affecting 40.3% (95% CI: 17.3–63.4), conductive hearing loss affecting 22.7% (95% CI: 5.7–39.7), and mixed or unspecified hearing loss affecting 34.5 (95% CI: 19.3–49.7) (Fig. 2).[4,10–24] When hearing loss was present, it was mild in 30.4% (95% CI: 10.8–50.1), moderate in 18.1% (95% CI: 11.3–25.0), moderate to severe in 22.0% (95% CI: 8.4–35.7), severe in 21.9% (95% CI: 13.3–30.7), and profound in 29.4% (95% CI: 16.4–42.3). A small external ear canal affected 26.9% (95% CI: 14.8–39.0) of patients, and low-set ears were reported in 41.8% (95% CI: 13.5–70.1) (Appendix 1).[2,5,11–29]

Five case series reported on middle ear anomalies.[19,23,30,32] Ossicular chain anomalies affected 57.2% (42.3–72.1) of patients.[19,23] More specifically, these included dysmorphism of the malleus and incus (large malleus head and incus body) in 12 of 20 ears and a bony cleft on the incus body in 10 of 20 ears in one case series.[19] Other middle ear anomalies were reported in nine of 10 patients and included hypoplastic mastoid in 12 of 20 ears and soft-tissue opacification of the tympanomastoid cavity in eight of 20 ears (Kim et al).[20] Both unspecified ossicular chain dysmorphism and soft-tissue opacification in the tympanomastoid cavity were reported in 40.6% (95% CI: 34.7–100) of patients without specification of the prevalence of either anomaly or whether they were found separately or in combination.[23] We found that 40.6% (95% CI: 34.7–100) of patients had unspecified middle ear anomalies.[29–31]

Inner ear anomalies were specifically mentioned in two case series with a prevalence of 40.6% (95% CI: 34.7–100) (Appendix 1).[19,23] These anomalies included incomplete-partitioned cochlea (9 of 20 ears), hypoplastic cochlea with modiolar deficiency (12 of 20 ears), an abnormally shaped vestibule with a focal protrusion at the posterioinferior aspect (15 of 20 ears), and facial nerve dehiscence in the tympanic and mastoid segments (3 of 20 ears) in one case series.[19] One patient of 32 (3.1%) had an incomplete-partitioned and hypoplastic cochlea with modiolar deficiency in another case series.[23] Finally, unspecified "ear anomalies" were reported 51.9% (95% CI: 21.9–91.8%) in three case series.[16,29,33]

Seven of the 34 case reports (Table III) mentioned hearing anomalies, with no new findings when compared to the case series.[34–40] Findings included CHL for two patients[35,39] and unspecified hearing loss for the remaining five cases.[33,34,36–38]

Infectious Manifestations

Ten case series reported on infectious manifestations in CdLS (Table II). Acute otitis media was the most prevalent infectious manifestation affecting 56.4% (95% CI: 34.1–78.4) of patients (Fig. 2).[14,17–19,22,41,42] Recurrent respiratory infections, including pneumonitis and bronchitis, were also prevalent and present in 44.1% (95% CI: 11.0–87.1) of patients (Appendix 2).[15,25,32,40–43] Two case series reported on rhinosinusitis disease affecting 36.1% (95% CI: 26.4–45.7) of patients.[19,40]

When reviewing case reports (Table III), five of the 34 cases mentioned infectious anomalies similar to those reported in the case series: recurrent pneumonia (2) and recurrent upper respiratory infections (2).[38,39,44,45] One patient was hospitalized for 5 months due to recurrent sepsis without mention of the etiology.[46]

Sleep Disorders

Nine case series reported on sleep disorders in the CdLS population (Table II). Obstructive sleep apnea (OSA) and obstructive sleep disordered breathing were the most widely reported disorders and were present in 25.8% (95% CI: 11.4–40.2) of patients (Fig. 2).[13,47,51] Insomnia was reported in one case series in which 42% (13 of 31) of patients had difficulty falling asleep and 45% (14 of 31) had difficulty staying asleep (Appendix 2).[52] In this study, insomnia and circadian rhythm dysfunction were evaluated in 31 patients using a sleep history questionnaire that focused on sleep patterns and behavior. This study found that difficulty falling asleep and maintaining

TABLE II.
Overview of the Otolaryngologic Manifestations of the Case Series of Patients With Cornelia de Lange Syndrome.

Author	Number of Patients	Newcastle Ottawa Quality Scale for Cohort Studies	Level of Evidence	Manifestations										
				Hearing Loss	External Ear Disorders	Middle Ear/Temporal Bone Disorders	Oral Cavity Anomalies	Sinus Anomalies	Sleep Anomalies	Airway Disorders	Voice Disorders	Craniofacial Anomalies	Infectious Disorders	GERD
Asahi et al. (2014)	2	Poor	4				X		X	X				
Barisic et al. (2007)	93	Poor	4		X		X			X*				
Begeman et al. (1976)	11	Poor	4		X		X					X	X	
Cates et al. (1989)	4	Poor	4											X
Egelund et al. (1987)	2	Poor	4	X								X		
Gibson (1964)	3	Poor	4		X	X	X				X	X	X	
Goodban (1994)	116	Poor	4	X							X			
Hamilton et al. (2014)	6	Poor	4	X	X		X		X	X				X
Hawley et al. (1995)	58	Poor	4	X			X					X	X	
Ichiyama et al. (1994)	2	Poor	4	X	X	X						X		
Ireland et al. (1993)	20	Poor	4	X	X		X					X		
Jackson et al. (1993)	246	Poor	4	X	X		X				X	X		
Janek et al. (2016)	35	Poor	4	X		X							X	
Jung et al. (2016)	32	Poor	4	X		X							X	
Jyonouchi et al. (2017)	45	Poor	4			X	X	X					X	X
Kaga et al. (1995)	10	Poor	4	X							X	X		
Kazuhiko et al. (1987)	4	Poor	4				X				X	X	X	
Kim et al. (2008)	10	Poor	4	X	X	X								
Kline et al. (2016)	49	Poor	4	X		X	X	X				X	X	
Kousseff et al. (1994)	2	Poor	4		X		X					X		
Marchisio et al. (2014)	44	Poor	4	X		X							X	
Marchisio et al. (2008)	50	Poor	4	X		X	X						X	X
Mariani et al. (2016)	73	Poor	4	X			X			X				X
Marres et al. (1989)	7	Poor	4	X	X	X	X					X		
Olioso et al. (2009)	45	Poor	4	X			X							X
Moeschler et al. (1993)	3	Poor	4		X							X	X	
Rohatgi et al. (2010)	32	Poor	4		X		X					X		
Sakai et al. (2002)	13	Poor	4	X										
Sataloff et al. (1990)	45	Poor	4	X	X	X	X						X	
Temtamy et al. (1994)	12	Poor	4	X	X		X					X		
Hall (2008)	54	Poor	4		X		X		X					
Berney et al. (1999)	49	Poor	4						X			X		
Zambrelli et al. (2016)	46	Poor	4						X					X
Rajan et al. (2012)	31	Poor	4						X					
Stavinoha et al. (2011)	22	Poor	4						X					

GERD = gastroesophagial reflux disorder; Newcastle Ottawa Scale = Assessing the Methodological Quality of Cohort Studies.

TABLE III.
Case Reports for Patients With Cornelia de Lange Syndrome.

Author	Hearing Loss	External Ears Disorders	Middle Ear/Temporal Bone Disorders	Oral Cavity Anomalies	Sinus Anomalies	Sleep Anomalies	Airway Disorders	Voice Disorders	Craniofacial Anomalies	Infectious Disorders	GERD
Callea et al. (2011)				X					X		
Chate (1994)		X		X			X		X		
Chowdhury et al. (2016)	X			X				X	X	X	X
Gadre et al. (1987)		X						X			
Gaur et al. (2016)		X		X			X		X		
Grau-Carbo et al. (2007)				X					X		X
Guadani et al. (2004)				X					X		
Gupta et al. (2005)		X		X					X		
Ingram et al. (2011)				X			X				
Kim et al. (2005)				X					X		
Kitenge et al. (2016)		X							X		
Meghwal et al. (2013)		X		X			X	X	X	X	
Moghaddam et al. (2008)	X	X						X	X		
Murray et al. (2012)	X	X							X		X
Noor et al. (2012)								X	X		X
Park et al. (2010)				X			X		X	X	X
Pulec et al. (1995)	X										
Russell et al. (2001)	X	X			X					X	X
Sasaki et al. (1996)			X								
Scarpelli et al. (2011)		X		X					X		X
Schuster (1988)				X							
Sen et al. (2015)							X		X	X	
Sonnenberg et al. (1980)		X		X				X	X		
Stevic et al. (2015)	X						X		X		
Sugiyama et al. (2012)							X				
Toker et al. (2009)		X		X					X		
Tsusaki (1998)			X				X				
Uzun et al. (2008)				X					X		
Vestergaard et al. (2015)	X						X	X	X	X	
Yamanobe et al. (2001)			X								
Mashaqi et al. (2017)						X					
Nechay et al. (2006)				X		X			X	X	
Reppucci et al. (2016)						X	X			X	
Stevenson et al. (1976)									X		

GERD: gastroesophageal reflux disorder.

TABLE IV.
Meta-analysis of Proportions of the Main Otolaryngologic Findings for Patients With Cornelia de Lange Syndrome.

	Mean Percentage (95% CI)	SE
Otologic findings		
Conductive hearing loss	22.7 (5.7-39.7)	8.7
Sensorineural hearing loss	40.3 (17.3-63.4)	11.8
Mixed/unspecified hearing loss	34.5 (19.3-49.7)	7.8
Narrow external auditory canal	26.9 (14.8-39.0)	6.2
Low set ears	41.8 (13.5-70.1)	14.4
Ossicular anomalies	57.2 (42.3-72.1)	7.6
Inner ear anomalies	40.6 (0-100)	38.4
Miscellaneous ear anomalies	51.9 (21.9-91.8)	15.2
Infectious disorders		
Acute otitis media	56.4 (34.1-78.4)	11.3
Rhinitis/sinusitis	36.1 (26.4-45.7)	4.8
Pneumonitis/bronchitis	44.1 (11.0-87.1)	21.9
Sleep disorders		
OSA/OSDB	25.8 (11.4-40.2)	7.3
Other sleep disorders	46.1 (13.2-79.0)	16.8
Gastrointestinal disorders		
Gastrointestinal reflux disease	58.0 (42.1-74.0)	8.1
Dysphagia	49.7 (25.9-73.6)	12.2
Voice and airway anomalies		
Dysphonia	76.6 (59.8-93.3)	8.5
Laryngomalacia	41.0 (0-100)	31.7
Choanal atresia	48.3 (0-100)	33.3
Miscellaneous airway anomalies	8.0 (1.0-15.0)	3.6
Facial plastic anomalies		
Small nose	73.9 (62.3-85.6)	5.9
Long philtrum	65.7 (44.8-86.6)	10.7
Anteverted nostrils	67.2 (50.0-84.5)	8.8
Depressed bridge	50.2 (36.1-64.3)	7.2
Micrognathia	53.1 (34.1-72.1)	19.0
Cleft palate	22.0 (15.1-28.8)	3.5
High arched palate	70.6 (56.5-84.8)	7.2
Orofacial cleft	27.5 (0-67.4)	20.4
Synophrys	95.2 (92.3-98.2)	1.5
Long eyelashes	87.1 (77.2-96.9)	5.0
Mouth anomalies	85.0 (76.2-93.8)	4.5
Eye anomalies	37.5 (18.8-56.2)	9.5
Lip anomalies	76.8 (65.3-88.4)	5.9
Dental disorders	65.1 (27.2-102.9)	19.3
Low hairline	64.2 (33.9-94.7)	15.5
Short neck	34.7 (0-96.6)	31.6

CI = confidence interval; OSA = obstructive sleep apnea; OSDB = obstructive sleep disordered breathing; SE = standard error

sleep affected 33% of adults and 52% to 75% of children with CdLS, indicating that circadian dysrhythmia is prevalent in this population.[51] Other unspecified sleep disorders were present in 46.1% (95% CI: 12.2–79.0) of patients.[32,48,50]

Sleep disorders were reported in three out of the 34 case reports reviewed, including sleep-disordered breathing (1), OSA (1), and skin dermatitis due to CPAP mask (1).[34,53,54]

Gastrointestinal Manifestations

Fourteen (14) case series reported on upper gastrointestinal manifestations in CdLS (Table II) (Fig. 3). GERD was the most widely reported on disorder, with a proportional prevalence of 58.0% (95% CI: 42.1–74.0).[4,5,11,13,19,26,41,46,47,49,55] Dysphagia or feeding difficulties were reported in 49.7% (95% CI: 25.9–73.6) of patients, and esophageal dysmotility was present in one case series for 13% (6 of 49).[4,5,9,13,15,19,25,26]

When examining the case reports, seven out of 34 cases reported GERD as a manifestation (Table III).[36,39,45,56,59] No new findings were mentioned.

Voice and Airway Disorders

Nine case series reported on various voice and airway disorders in the CdLS population (Table II) (Fig. 3). The majority of patients presented with a voice disorder commonly described as a high-pitched voice in 76.6% (95% CI 59.8–93.3).[5,24,26,40]

One case series found articulation deficiencies in 12% (12 of 49) of patients.[19] Airway disorders were infrequently reported in case series. Manifestations included choanal atresia, laryngomalacia, and difficult exposure during intubation. Choanal atresia causing obstructive breathing was present in 48.3% (95% CI: 17.0–100) and laryngomalacia in 41.0% (95% CI: 39.3–100.0) (Appendix 2).[2,4,13] A case series of two patients noted difficult airway exposure during intubation in 50% (grade 3 exposure).[42] Death secondary to aspiration or apnea occurred in 2% (6 of 310) in one case series.[5]

The most important new findings by reviewing case reports were the airway disorders that were mentioned in 11 patients.[2–5,37,57,60–64] Airway manifestations included hypoxia and cardiac arrest (n = 1), difficult mask ventilation (n = 1), difficult airway visualization with intubation: grade 3 or 4 exposure view (n = 4), postoperative respiratory distress (n = 1), upper airway obstruction with tracheostomy (n = 1), laryngeal anomalies not otherwise specified (n = 1), reactive airway disease (n = 1), and facial contact dermatitis (n = 1).

Oral Cavity and Dental Disorders

Twenty-three (23) case series reported on oral cavity and dental disorders in CdLS patients (Table II). The vast majority of patients presented with dental anomalies 65.1 (95% CI: 27.2–100), including recurrent dental carries and impaction (Appendix 2).[5,11,12,15,31,40,42,49] Palate abnormalities were also fairly common, with cleft palate affecting 22.0% (95% CI: 15.1–28.8) and high arched palate affecting 70.6% (95% CI: 56.5–84.8) (Fig. 4).[2,4,13,15,17,19,24,31,32,40–42] Orofacial clefts presented in 27.5% (95% CI: 12.4–67.4) of patients.[2] Unspecified lip anomalies presented in 76.8% (95% CI: 65.3–88.4%), and mouth shape abnormalities, most commonly crescent mouth, presented in 85.0% (95% CI: 76.2–93.8).[5,8,9,13,19,23,24,26–28,40,42] One case series

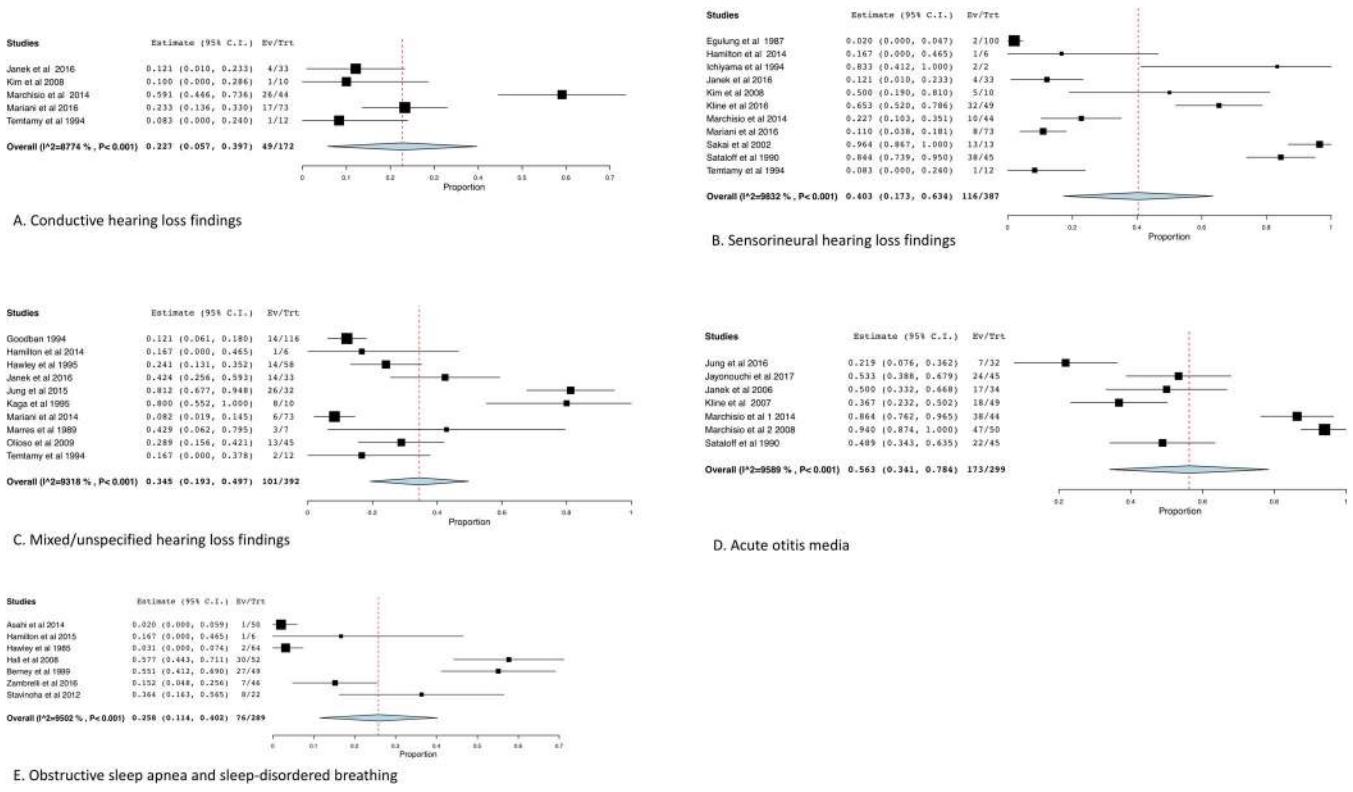

Fig. 2. Results of meta-analysis of proportions for hearing findings (A, B, C), acute otitis media (D), and obstructive sleep apnea (E).

identified macrostomia in 16.7% (2 of 12) and fissured tongue in 33.3% (4 of 12) of included patients.[12]

Similarly, oral cavity and dental disorders were also frequently reported in 17 out of the 34 case reports (Table III).[19,24,39,43,45,55,57,60,61,65,72] Manifestations included nonerupted anchylosed teeth (n = 1), teeth in ectopic position (n = 3), delayed eruption (n = 5), cleft palate (n = 5), thin and downturned lips (n = 8), anodontia (n = 3), widely spaced teeth/incisors (n = 1), periodontal illness (n = 1), persistence of temporal teeth (n = 1), wide open-bite (n = 2), high arched palate (n = 4), class II or III malocclusion (n = 2), macrodontic deciduous teeth (n = 1), hypomineralized areas on the vestibular surfaces of deciduous cusps and molars (n = 1), protruded maxillary anterior teeth (n = 1), velopharyngeal insufficiency with no cleft (n = 1), occlusal attrition (n = 1), and microdontia (n = 1).

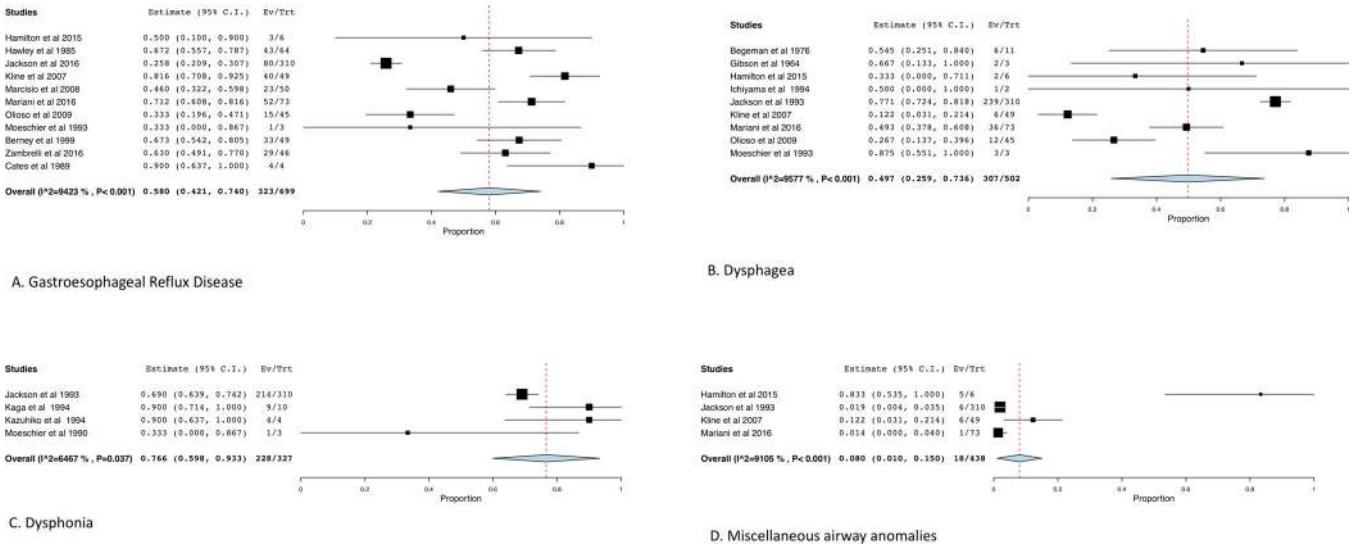

Fig. 3. Results of meta-analysis of proportions for gastroesophageal reflux disease (A), dysphagia (B), dysphonia (C), and miscellaneous airway anomalies (D).

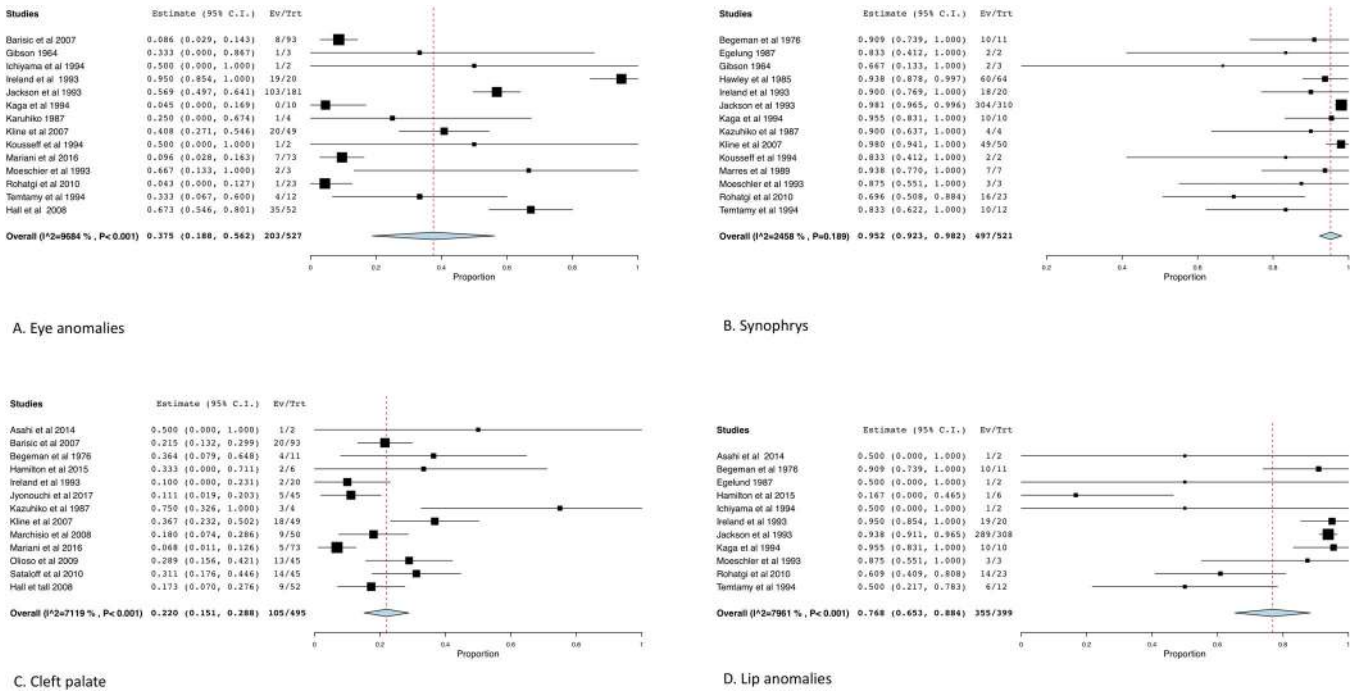

Fig. 4. Results of meta-analysis of proportions facial and esthetic findings.

Craniofacial Manifestations

Twenty case series reported on various craniofacial manifestations in the CdLS population (Table II). Almost all patients had synophrys at 95.2% (95% CI: 92.3–98.2); long philtrum in 65.7% (95% CI: 44.8–86.6%); and long, thick eyelashes in 87.2% (95% CI: 77.2–96.9) (Fig. 4).[5,7,10,11,14,16,18,22,27,34] Nasal abnormalities included small nose reported in 73.9% (95% CI: 62.3–85.6), anteverted nostrils in 67.2% (95% CI: 50.0–84.5), and a depressed nasal bridge in 50.2% (95% CI: 36.1–64.3).[4,7,11,14,16,18,22,27,34] Micrognathia was present in 53.1% (95% CI: 34.1–72.1) of patients.[4,9,11,14,16,22–25,27,34,35] Eye anomalies overall affected 37.5% (95% CI: 18.8–56.2) of patients.[2–4,11,14,16,22,24,27,31,34,40] Other abnormalities noted were a low hairline in 64.2% (95% CI: 33.9–94.7) and a short neck in 34.7% (95% CI: 27.1–96.6) (Appendix 3).[2,4,7,11,22–27]

In the case reports, craniofacial anomalies (23 cases) were the most prevalent manifestations and were similar to those reported in the case series.[24,35–39,43–45,55–57,60,61,63,65–70,73–76]

Findings included synorphys (n = 15); long, thick eyelashes (n = 12); anteverted nares (n = 12); crescent-shaped lip (n = 13); and a long philtrum (n = 11). One new finding reported was the presence of an antimongoloid slant in two patients.[35,70]

DISCUSSION

In this systematic review, we present data from 35 eligible case series and 34 case reports regarding otolaryngologic disorders in patients with CdLS. The main findings included craniofacial anomalies, hearing loss, and dental anomalies. Additional anomalies included infectious, sleep, and gastrointestinal and voice manifestations. Although infrequently discussed in the past, this review included a study of airway anomalies noted in the operating room, findings that deserve further future investigation.

Otologic Manifestations

Consistent with reports in the literature, almost all patients had some degree of hearing loss, with SNHL being most common, followed by CHL and unspecified hearing loss. Evaluation of hearing loss has been a challenge in this population due to issues with cooperation and developmental delay.[14,77] Pure-tone audiometry, free-field audiometry, and brainstem auditory evoked potential have been described as ways to assess hearing loss.[10,11,14,71] Interestingly, the severity of hearing loss was infrequently reported and ranged from mild to profound. Data were found in 13 case series, with approximately one-third of patients having mild hearing loss and one-third having severe-to-profound hearing loss. With regard to conductive hearing loss, possible etiologies include external ear canal stenosis, middle ear ossicular anomalies and otitis media, either acute or chronic. Otitis media affects over half of patients and is a potential reversible cause of hearing loss in these individuals. Other possible hearing loss causes include inner ear anomalies such as cochlear dysplasia. A few case reports discussed unspecified middle ear anomalies, which were either unspecific soft tissue filling the middle ear or a small middle ear space or were undescribed anomalies. Imaging studies were sometimes reported, mostly when patients had otologic symptoms and were performed at the physician's discretion. Thus, the real incidence of

temporal bone anomalies is likely underestimated. Only a few studies report on the management of hearing loss in this population. Poor compliance with hearing aid fitting is the major hurdle preventing these patients from obtaining a serviceable hearing improvement. Compliance with hearing aid fitting is also often reported to be very low, whereas the incidence of patients lost to follow-up is high.[23] Furthermore, the tolerability of hearing aids has not been systematically described in this population but seems to be low. Interestingly, a few case series report on the outcomes of cochlear implantation for these patients, with inconsistent outcomes.[10,23] Moreover, Janek et al. (n = 78) described an improvement in hearing loss in 14% of patients over time, with 6% experiencing complete resolution despite some being diagnosed with profound sensorineural hearing loss as young children.[22,23] The authors suggested that auditory neuropathy should be considered in these patients and that longitudinal follow-up of these patients is warranted. Jung et al. (n = 32) reported a series of seven patients with no improvement after the placement of pneumatic ear tube despite conductive hearing loss primarily due to soft tissue identified in the middle ear.[24] These authors concluded that ear tube placement was not effective to eradicate middle ear disease or improve conductive hearing loss in such patients. Despite their conclusions, ear tube placement still seems appropriate for first-line management of CHL in patient with suspicion for middle ear effusion.

However, hearing loss investigation and management should be individualized based on patient comorbidities, delay, and caregiver concerns because repeats of patients using hearing aids, BAHA, and CI have all demonstrated some degree of success.

Infectious Manifestations

Our results suggest that patients with CdLS may be more susceptible to infections when compared to the general population, with otologic and respiratory infections reported most frequently. Over half of patients reported having either acute otitis media or recurrent upper and/or lower airway infections. Because hearing loss is common in these patients, identifying reversible causes such as otitis media would be important to minimize language delay in these patients. Interestingly, patients with CdLS report a high prevalence of recurrent airway and respiratory infections, including pneumonia and bronchitis. GERD and dysphagia are also known to be highly prevalent in these children. However, it is unknown if these underlying issues may contribute to recurrent respiratory infections due to aspiration. Furthermore, Jyonouchi et al. (n = 45) were the first to report underlying immunodeficiency in patients with CdLS.[42] They concluded that all patients with CdLS and a history of recurrent infections should undergo an immune evaluation. These authors recommended that testing include total immunoglobulin levels (IgG, IgM, IgA), antibody titers to vaccine antigens (tetanus, diphtheria, pneumococcus), and a complete blood count with differential. Because these infections carry a high risk of morbidity, early identification of any predisposing immunity issues is important for the management and counseling of these patients.[41]

Sleep Disorders

Insomnia and OSA/SDB were the sleep disorders reported most frequently. Consistent with recent reports, OSA is common in CdLS patients and more commonly reported than in the general population. OSA has been associated with numerous neuropsychiatric and cardiopulmonary sequelae, making it a great concern for patients with CdLS already at increased risk for behavioral and intellectual disorders. Recognizing that OSA may be more common in patients with CdLS is important because management strategies including continuous positive airway therapy, nasal and oral appliances, and upper airway surgery have been shown to be effective treatments for OSA. However, there is limited information regarding management in this population. Because this review suggests that sleep disorders can affect a significant number of these patients, polysomnography may be beneficial to assess patients with symptoms of sleep disorders. Additionally, insomnia and circadian rhythm disorders were prevalent in this population, which may contribute to significant impairment in the development and quality of life of these children.

There is little to no information regarding the effectiveness of sleep surgery with polysomnographic outcomes in this population. In addition, drug-induced sleep endoscopy (DISE) has not been studied in this population. However, given the complexity of these patients, DISE might be useful to provide information about the site(s) of obstruction and to tailor surgery for the specific site(s) of obstruction.[78] Moreover, parents would ideally be involved in the decision making regarding the optimal medical or surgical management of sleep disorders.[79,80] Finally, OSA should not be overlooked in this population because treatment has proven to improve patient and family quality of life in both typical children and those with syndromes; the same conclusion could reasonably be extrapolated to this population.[81,82]

Gastrointestinal Manifestations

For patients with CdLS, gastrointestinal manifestations are also frequently reported. Manifestations relevant to otolaryngology include GERD and feeding/swallowing difficulties. A case series by Hamilton et al. (n = 6) reported a patient who suffered from laryngeal overspill leading to choking attacks secondary to GERD, which was refractory to medical and surgical management.[50] Given the high prevalence of GERD, there is concern that these patients will have difficulty with adequate nutrition, chronic laryngitis, and aspiration. Additionally, the efficacy of medical therapy, such as a proton-pump inhibitor, is yet to be systematically studied in this population. This review also identified a high likelihood of feeding difficulties due to nonspecific dysphagia, GERD, esophageal dysmotility, or other unspecified cause. These manifestations are concerning because they may contribute to an increased risk of aspiration and failure to thrive. Moreover, strategies to improve these feedings issues, such as gastrostomy tube placement and/or institution of a modified diet, are yet to be described on a large scale. However, for a more severe gastrointestinal manifestations, such as failure to thrive

and life-threatening aspiration pneumonia, Cates et al. (n = 4) reported successful management with anti-reflux procedures (Nissen fundoplication) and concomitant feeding gastrostomy.[55]

Patients with CdLS have a high frequency of gastrointestinal problems, with GERD being the most common manifestation. Patients should have a comprehensive workup of their symptoms and receive aggressive treatment of reflux, including consideration of medical and surgical treatments, to prevent further morbidity.

Voice and Airway Disorders

It is well described in the literature that these children may have a high-pitched cry that is consistent with our data showing a prevalence of 70% among CdLS infants. Airway anomalies are not restricted to the quality of the voice but also to the ability of these children to use language at an "age-appropriate" level. A study with 116 patients (Goodban) had three overall findings regarding language skills of the patients with CdLS: 1) their ability to produce language was inferior to their ability to comprehend language; 2) there was a discrepancy between vocabulary skills and syntactic skills; and 3) almost all patients with CdLS were unusually quiet and talked only minimally.[14] These findings prompted calls for optimal care of these patients to begin with an interdisciplinary team evaluation. This team should include an audiologist to optimize hearing and a speech pathologist to assist with communication skills. Airway abnormalities identified included choanal atresia and laryngomalacia. However, the population of patients in whom the presence of choanal atresia was assessed was small, and thus it is difficult to assess the actual prevalence of this manifestation. Laryngomalacia appears to be a notable airway abnormality in CdLS. Because both anomalies may result in a risk of airway obstruction and hypoxia in children, evaluation of these abnormalities is important. In addition, surgical management is often effective in relieving obstruction for both these conditions, and thus early identification may be extremely useful to drive management.

It is suspected that patients with CdLS may present with a higher American Society of Anesthesiologists grade and thus increased airway risk during anesthesia when compared to typical children due to a higher prevalence of obstructive disorders such as OSA, laryngomalacia, and choanal atresia. In addition, there are limited reports suggesting that these children are harder to intubate than typical children. However, there is a paucity of data regarding intubation difficulties in patients with CdLS. In addition, death due to aspiration and/or apnea has been reported in six children, again highlighting the importance of early identification of airway abnormalities in these patients. Few reports also noted that these patients had a grade 3 or 4 exposure, making intubation difficult and resulting in the use of a nasal fiber optic fiber, glide scope, or cricoid pressure to intubate these patients.[38,44,62,64] Several factors may explain a harder exposure, including the presence of a cleft palate, restricted mouth opening, dental anomalies, and micrognathia—all of which are present more than 50% of the time for these children. Strategies for intubation included cricoid pressure, use of a stylet, fiberoptic intubation, and pediatric video laryngoscope. Furthermore, difficult ventilation was infrequently reported for one patient in the case reports; it should be considered because it can result in significant issues for these patients. This more difficult ventilation was relieved with the placement of an oral airway.[62]

Oral and Dental Disorders

Palate and dental abnormalities are well-recognized manifestations of CdLS, which is consistent with our results. The majority of patients presented with some form of dental or periodontal disease, including dental carries, erosions, and impaction. The high prevalence of dental disease in this population is interesting given the high frequency of GERD in our review, a known risk factor for enamel disease. Additionally, intellectual disability with an impaired ability to perform activities of daily living, including maintaining dental hygiene, may contribute to this phenomenon. Other important dental manifestations include a high reported prevalence of microdontia, delayed tooth eruptions, and partial anadontia. Based on these findings, we would suggest that close care and follow-up by dental experts should be encouraged for these patients.

The most common palatal abnormalities were high arched palate followed by cleft palate. Palate abnormalities can frequently result in impaired speech, swallowing, and breathing, making identification and correction critical. Furthermore, palatal abnormalities can negatively impact the ability to easily intubate a patient. Whereas cleft palates are typically obvious at birth, a high arched palate may not be as obvious. A heightened index of suspicion for a high arched palate may be important because this abnormality may result in narrowing of the airway and SDB as well as speech and swallowing disorders.

Craniofacial Manifestations

The craniofacial appearance of CdLS patients is quite consistent and has been extensively described in the literature with characteristics that includes synophrys; long, thick eyelashes; anteverted nostrils; and low hairline. Micrognathia is also common, which may negatively impact the patency of the airway. We also found that a long philtrum was present in the vast majority of patients, which is also a defining feature of fetal alcohol syndrome and may contribute to the fact that milder cases of CdLS may sometimes be confused with fetal alcohol syndrome.[71] Other less well-recognized reported features include a short neck and eye anomalies. The latter has been reported in several studies and includes a wide range of manifestations, such as hypertelorism, ptosis, recurrent blepharitis, and epicanthal folds. Ocular manifestations were present in a high number of patients. They are often more subtle than other craniofacial manifestations but should also be assessed.

Limitations and Future Direction

Our systematic review is limited by the quality of published papers in this area; this evidence is limited to case reports and case series (level 4 evidence). Despite this, we

were able to assess 69 studies. Moreover, randomized control trials would be difficult to perform given the nature and relative prevalence of the disorder. It is possible that some manifestations such as airway exposure during intubation were underreported because they were not specifically evaluated. In addition, some studies were not specific in their reporting and included anatomic and functional conditions such as "ear problems," which may include hearing loss or external anatomic deformities, in the same category. Finally, some of the studies reported on the presence or absence of associated symptoms and conditions based on caregiver-completed surveys, which may result in over- or underreporting. Nonetheless, this is the most comprehensive and the first systematic review of otolaryngology manifestations in CdLS.

This systematic review may also be limited by the presence of bias despite adherence to the PRISMA recommendations during our literature review. The potential for reporting bias is significant because children with symptoms or findings are more likely to be reported. In addition, one of the inclusion criterions was "the mention of otolaryngology manifestations," which may have resulted in selective inclusion of studies that significantly reported these findings, which could further bias the results of the review toward positive findings. Additionally, there is also potential for evidence selection bias because our review only included published manuscripts, which may bias our review toward positive findings. Moreover, the quality of the studies was overall classified as poor because all but one study lacked a comparison group, although the quality scores for patient's selection and outcomes were often high. Lastly, it is possible that some patients may have been overlapping between studies, which could lead to overreporting of findings.

Ideally, future reports will include negative findings to ensure that we can determine true prevalence. It would also be valuable to report less frequent but significant manifestations such as airway disorders. Lastly, there is a significant need to report on the success or failure of current management option for these conditions in these patients.

CONCLUSION

In this systematic review of the CdLS literature, we found otolaryngologic manifestations to be numerous. The most frequent manifestations included hearing loss (conductive, sensorineural, mixed), recurrent infections (acute otitis media, upper/lower airway infections), sleep disorders, dysphagia, voice disorder, and craniofacial anomalies (anteverted nostrils; micrognathia; synophrys; long, thick eyelashes). Airway disorders were primarily reported in case reports but included significant issues with difficult intubation and/or ventilation, which suggests that further examination is needed in this area. In addition, there was little information published regarding the effectiveness of standard management options for otolaryngology-related diseases for these children.

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