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Review articles

Audiological profile of individuals with Cornelia de Lange syndrome: an integrative review

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ABSTRACT

Purpose: to describe the audiological profile of patients with Cornelia de Lange syndrome (CdLS) in an integrative review of the literature.

Methods: after developing the research question, articles were searched in six databases (EMBASE, ISI of Knowledge, LILACS, MEDLINE/PubMed, SciELO, and Scopus) and in sources of information (Google Scholar, OpenGrey, and ProQuest), with the following descriptors: audiology, hearing loss, deafness, hearing disorders, and Cornelia de Lange syndrome. This review was registered in Prospero under number CRD42020191481. National and international studies were considered for analysis, using the PECO acronym. The risk of bias in the studies was analyzed with Joanna Briggs Institute protocols. Then, the studies were described and analyzed.

Results: of the 1,080 articles found, 12 met the inclusion criteria. Audiological results showed that individuals with CdLS can have hearing loss – conductive hearing losses were the most frequent impairments, corresponding to 49.20% of individuals with CdLS assessed, followed by sensorineural hearing losses (13.49%). The degrees of hearing loss ranged from mild to profound.

Conclusion: individuals presented with CdLS often have hearing loss, mainly due to middle ear changes, with degrees ranging from mild to profound.

Keywords: Audiology; Hearing Loss; Brainstem Auditory Evoked Potentials; Cornelia de Lange Syndrome

INTRODUCTION

Cornelia de Lange syndrome (CdLS), also known as Brachmann-de Lange syndrome, is a rare genetic heterogeneous disease. It affects the functioning of multiple organs and systems[1], with phenotypes ranging from mild to severe, possibly leading to death[2].

The first cases were reported in 1849 by anatomists Gerardus and Willem Vrolik, and in 1916 and 1933, Brachmann and Cornelia de Lange described and named the syndrome. They observed the patients' distinct facial characteristics, upper and/or lower limb abnormalities, intellectual disability, behavioral changes, and associated malformations (cardiac, gastrointestinal, and musculoskeletal)[1]. CdLS incidence is estimated at 0.5-10 per 100 thousand[3], although the exact incidence is unknown because many mild cases tend to be underreported[1,3].

Most cases originate from genetic mutations, with no distinction of sex, race, or ethnic origin[4]. Up to the present, genetic mutations that reflect CdLS phenotypes are known to occur in five specific genes: NIPBL (80% of cases), SMC1A (5% of cases), HDAC8 (4% of cases), SMC3 (1–2% of cases), and RAD21 (< 1% of cases). Diagnosis is based on clinical findings and/or identification of a pathogenic heterozygous variant in NIPBL, RAD21, or SMC3 or a pathogenic homozygous variant in HDAC8 or SMC1A[1,5].

Among other factors, these genetic impairments can cause hearing loss of either syndromic or non-syndromic origin. It can be transmitted through dominant autosomal (15%), recessive autosomal (80%), sex-related (2-3%), and mitochondrial patterns (1-2%)[6].

Findings in the literature indicate that hearing loss is very common (85–90%) in individuals with CdLS from childhood. They are predominantly bilateral, ranging from mild to severe (40–50%); conductive hearing loss can occur in 75% of cases, while sensorineural hearing loss occurs in 25% of cases. In adults, sensorineural hearing loss is reported in 45% of individuals with CdLS[7].

The scientific literature describes that the hearing functioning impairment in this syndrome is due to structural anomalies in various regions of the auditory system, including the outer, middle, and inner ears[7]. Hence, possible conductive hearing loss etiologies include external acoustic meatus stenosis, middle ear ossicular anomalies, acute or chronic otitis media, and even the presence of nonspecific soft tissues filling in the middle ear. Possible sensorineural hearing loss etiologies can be ascribed to inner ear anomalies, such as cochlear dysplasia[7-9].

Since both conductive and sensorineural hearing loss can negatively impact these individuals' development, they need a multidisciplinary approach, with routine audiological examinations. Medical procedures include surgical (ventilation tubes) and nonsurgical treatment, and/or the indication, selection, and fitting of hearing aids. These must be considered to maximize speech and language development through early amplification in children; in the case of adults, they provide greater interaction between patients and family/friends and effective communication in the workplace, improving the quality of life of patients and family[10].

Nevertheless, little is yet known about the audiological profile in CdLS[11]. Thus, scientific research data on the audiological profile and hearing loss incidence in this population must be surveyed to implement guidelines. These can be then followed in clinical routine diagnostic assessments and direct future studies.

Hence, this study aimed at describing the audiological profile of patients with CdLS through an integrative review of the literature. The research was outlined based on the following research question: "What is the audiological profile of patients presented with CdLS?"

METHODS

This integrative review of the literature was registered in Prospero under number CRD42020191481.

Eligibility criteria

National and international studies were considered for analysis in this review, with no restriction on language or year of publication. The PECO[12] acronym directed the search as follows:

- **Patient:** individuals with CdLS. Given the rarity of the syndrome, there was no restriction on sex or age.
- **Exposure:** audiological assessment, including acoustic immittance, pure-tone threshold audiometry (PTA), otoacoustic emissions (OAE), and/or brainstem auditory evoked potentials (BAEP).
- **Comparison:** control group results (individuals without the syndrome), comparison according to normal criteria defined in the literature or studies with no comparisons.
- **Outcomes:** having audiological changes or not. When changes were present, data on the type,

degree, configuration, and incidence of hearing loss were collected.

Exclusion criteria

Studies assessing other syndromes, not clearly describing the procedures or audiological characterization data, expert opinions or scientific event abstracts not presenting methodological data with sufficient information, and studies not answering the research question were excluded.

Sources of information, databases, and search strategy

This review was based on the search for studies published in the databases: EMBASE, ISI of Knowledge, Lilacs, MEDLINE/PubMed, SciELO, and Scopus, and in the sources of information: Google Scholar, OpenGrey, and ProQuest.

Descriptors were selected by consulting the Health Science Descriptors (DeCS) and Medical Subject Headings (MeSH) in both English and Portuguese. Specific search strategies were used for each database and source of information (Appendix 1).

The search was performed on a single day (March 17, 2020) and later updated (September 6, 2021) in all databases, not using any filter. The Endnote Clarivate platform was used to gather all retrieved references for analysis.

References in studies selected for full-text reading were analyzed and experts in the field were consulted to complement the search and identify other potentially eligible studies.

The author of studies unavailable in full text on electronic platforms was contacted (via e-mail or ResearchGate platform) to verify the possibility of having them send the manuscript.

Study selection criteria and data collection

After the bibliographical survey, duplicate studies were automatically excluded by Endnote[13]. They were manually searched afterward to verify whether other duplicates remained.

Then, the titles were read, and those that possibly answered the research question were selected to have their abstracts read. After reading the abstracts, the eligible ones for full-text reading were selected. After reading the full texts, those that met all previously established eligibility criteria were selected.

Two independent reviewers (NPS and LAFS) conducted each of these stages (title, abstract, and full-text reading). When they finished each stage and before continuing to the next one, the data were compared. If there were divergences, a third reviewer (CGM) was consulted; the three researchers made decisions by discussing the issue and reaching a consensus.

The following relevant data were extracted from the selected studies for analysis: author and year of publication, country of origin, objective, sample (number, age range, sex, syndrome diagnostic criteria), procedures used (types of procedures and normal criteria), results, and main conclusions. In the case of longitudinal studies, the results of the first assessment were considered.

Data analysis

The risk of bias in each study was analyzed with standardized protocols developed by the Joanna Briggs Institute, which help assess the reliability, relevance, and results of published papers[14]. Then, the studies were qualitatively described and analyzed.

LITERATURE REVIEW

Results in databases

The search identified 1,080 references, most of them retrieved from OpenGrey. After excluding repeated references, 859 studies were left.

Considering the inclusion criteria, 859 titles were read. In this stage, 818 studies were excluded; hence, 41 abstracts were read. After reading the abstracts, 21 studies were eligible for full-text reading. Then, having read the full texts and analyzed their risk of bias, nine articles were excluded: two for not clearly presenting the results[15,16]; three for having nonspecific methodologies[17-19]; three for not answering the research question/objective[20-22]; and one for not having the full text available, even after contacting the author[23] (Appendix 2). Thus, 12 articles were selected for analysis in this review (Figure 1).

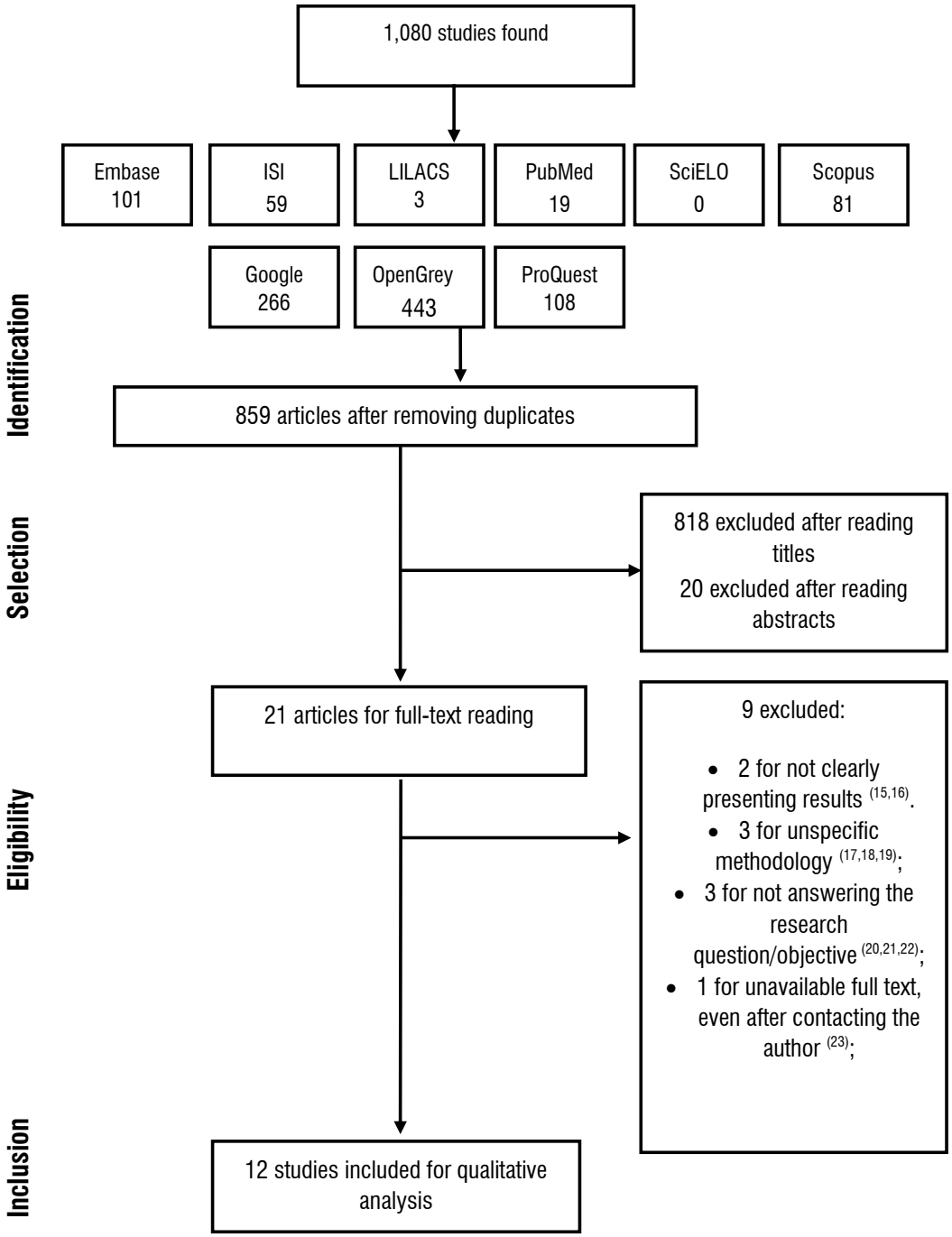

Figure 1. Flowchart with article selection

Methodological characteristics of studies included in the review

After the bibliographical survey and study selection, extracted data were summarized. Methodological data are shown in Chart 1 and results are shown in Chart 2.

The risk of bias of each article was analyzed according to the study type: five of them were case reports[24-28] (Table 1), four were cross-sectional observational studies[9,10,29,30] (Table 2), and three were case series[8,31,32] (Table 3).

Chart 1. Summary of methodological aspects of each study (n = 12)

Reference	Country of origin	Type of study	Sample			CdLS diagnostic criteria	Audiological procedures	Normal criteria
			Size	Sex	Age range			
Chowdhury et al., 2016[27]	India	Case report	1	M	8 years	Specific phenotypical characteristics of the syndrome	Acoustic immittance, PTA, DPOAE, BAEP	NS
Egelund., 1987[24]	Denmark	Case report	2	1 M; 1 F	Approximately: (M) - 19 years; (F) - 10 years	Specific phenotypical characteristics of the syndrome	Acoustic immittance, PTA, BAEP	NS
Ichiyama et al., 1994[25]	Japan	Case report	2	2 M	(1): NS; (2): 2 years	Specific phenotypical characteristics of the syndrome	BAEP	NS
Janek et al., 2016[30]	United States	Cross-sectional observational	78	39 M; 39 F	7 months to 50 years	NS	PTA	Mild (21-40 dB); moderate (41-65 dB); severe (65-90 dB); profound (> 90 dB)
Jung et al., 2016[9]	Korea	Cross-sectional observational	32	12 M; 20 F	0 to 10 years	NS	Acoustic immittance, BAEP	BAEP worst ear ET: mild 25-40; moderate 40-55; moderate/severe 55-70; severe 70-90; profound >90
Kaga et al., 1995[31]	Japan	Case series	10	5 M; 5 F	7 months to 14 years	Specific phenotypical characteristics of the syndrome	PTA, BAEP	NS
Kim et al., 2008[8]	Korea	Case series	10	4 M; 6 F	7 months to 8 years	NS	PTA, BAEP	PTA up to 25 dB and BAEP with ET up to 40 dBnHL
Marchisio et al., 2008[10]	Italy	Cross-sectional observational	50	23 M; 27 F	1 to 18 years	Each child confirmed by a geneticist specializing in this syndrome	Acoustic immittance, PTA, BAEP	PTA: discrete (21–25 dB); mild (26–40 dB); moderate (41–65 dBHL) or severe (65–90 dBHL); Acoustic immittance Jerger, 1970.
Marchisio et al., 2014[29]	Italy	Cross-sectional observational	44	22 M; 22 F	1 to 17 years	Clinical signs and symptoms and genetic tests (NIPBL and SMC1A gene detection)	Acoustic immittance, PTA, BAEP	PTA: discrete (21–25 dB); mild (26–40 dB); moderate (41–65dBHL) or severe (65–90 dBHL); Acoustic immittance Jerger, 1970.
Sakai et al., 2002[32]	Japan	Case series	13	6 M; 7 F	3 months to 4 years	Extensive genetic assessment for confirmation	PTA, BAEP	NS
Oikawa et al., 2015[28]	Japan	Longitudinal case report	1	M	1 month	Characteristics of the syndrome	PTA, DPOAE, BAEP	NS
Oliveira de et al., 2009[26]	Brazil	Case report	1	F	8 years and 7 months	Genetic assessment and observation of facial anomalies	Acoustic immittance, OAE, BAEP	NS

Captions: SG – study group; CG – control group; CdLS – Cornelia de Lange syndrome; HL – hearing loss; PTA – pure-tone threshold audiometry; OAE – otoacoustic emissions; M - males; F - females; DPOAE – distortion-product otoacoustic emissions; TEOAE – transient-evoked otoacoustic emissions; BAEP – brainstem auditory evoked potential; AC – air conduction; BC – bone conduction; CHL – conductive hearing loss; SNHL – sensorineural hearing loss; RE – right ear; LE – left ear; ET – electrophysiological threshold; Lat - latency; MHL – mixed hearing loss; ME – middle ear; Abs. - absence; Pres. - Presence; NL - normal; NS – Not specified; NP – Not performed.

Chart 2. Summary of main results of each study (n = 12)

Reference	Results					
	Acoustic immittance measures	Incidence of HL	PTA		OAE	BAEP
			Type of HL	Degree of HL		
Chowdhury et al., 2016[27]	Bilateral type B	100% (case study)	CHL	Mild (mean 36.6 dB in RE and 33.3 dB in LE)	NS	Click BAEP at 40 dBnHL ET (AC) and up to 20 dBnHL (BC)
Egelund., 1987[24]	M: bilateral type A and pres. reflexes; F: bilateral type A	100% (both subjects had HL)	SNHL	Mild	NP	M: NP; F: bilateral SNHL. ET in RE at 55 dB
Ichiyama et al., 1994[25]	NP	100% (both subjects had HL)	NP		NP	(1): abs. responses at 100 dBnHL. (2): wave I and interpeak interval I-V with normal lat. ET at 40 dBHL
Janek et al., 2016[30]	NP	67%	33.3% SNHL 33.3% CHL 33.3% MHL	17.6% mild 29.4% moderate 29.4% severe 23.5% profound	NP	NP
Jung et al., 2016[9]	Measured in 14 subjects: 13 type B; 1 bilateral type A	81.2%	NP		NP	18.8% NL; 6.3% mild HL; 15.6% moderate HL; 31.3% moderate/ severe; 12.5% severe; 15.6% profound
Kaga et al., 1995[31]	NP	100%	NS	10% moderate 90% profound	NP	80% abnormal BAEP: 40% bilateral severe HL, 20% unilateral severe HL, 20% bilateral mild HL
Kim et al., 2008[8]	NP	60%	Performed in 2 patients: 1 CHL and 1 NL	Mild	NP	10% mild 10% profound 40% various degrees
Marchisio et al., 2008[10]	NS	80%	10 subjects (20%) MHL 30 subjects (60%) CHL	MHL: Discrete in 1 (23 dB); mild in 4 (23–33 dB), moderate in 4 (52–60 dB), severe in1 (65 dB); CHL: Discrete in 11 (21-24 dB); mild in 16 (21-38 dBHL), moderate in 3 subjects (45–50 dBHL)	NP	NS
Marchisio et al., 2014[29]	NS	81.8%	SNHL = 22.7% CHL = 59.1%	45.4% = discrete/mild 36.4% = moderate/severe	NP	NS
Sakai et al., 2002[32]	NP	100%	NS	Moderate to severe HL = 100%	NP	46.15% - abs. responses (33.3% = pres. responses in subsequent years); 15.38% - bilateral pres. responses; 23.07% = unilateral abs. responses; 15.38% wave V abs. in 1 ear, BAEP NL in the other
Oikawa et al., 2015[28]	NP	100%	SNHL	Moderate HL, improving over time. Final assessment with a mean 0.5, 1, and 2 kHz between 20 and 35 dB	1st month: DPOAE = abs. in RE and pres. in LE; 2nd month: DPOAE = pres. in RE and abs. in LE	BAEO ET at 3 months = 70 dB/RE and 70 dB/LE; 8 months - 70 dB/RE and 60 dB/LE; 1 year - 50 dB/RE and 60 dB/LE; 4 years and 1 month: BAEP NL
Oliveira de et al., 2009[26]	Bilateral type B and abs. reflexes	100%	NP		TEOAE and DPOAE = bilaterally abs.	BAEP ET: RE = 80 dBnHL and LE = 80/90 dBnHL; BAEP with bilaterally increased absolute lat. and normal interpeak intervals

Captions: SG – study group; CG – control group; CdLS – Cornelia de Lange syndrome; HL – hearing loss; PTA – pure-tone threshold audiometry; OAE – otoacoustic emissions; M - males; F - females; DPOAE – distortion-product otoacoustic emissions; TEOAE – transient-evoked otoacoustic emissions; BAEP – brainstem auditory evoked potential; AC – air conduction; BC – bone conduction; CHL – conductive hearing loss; SNHL – sensorineural hearing loss; RE – right ear; LE – left ear; ET – electrophysiological threshold; Lat - latency; MHL – mixed hearing loss; ME – middle ear; Abs. - absence; Pres. - Presence; NL - normal; AI – acoustic immittance; NS – Not specified; NP – Not performed.

Table 1. Analysis of the risk of bias of case reports with the Joanna Briggs Institute protocol

	Egelund, 1987[24]	Ichiyama et al., 1994[25]	Oliveira de et al., 2009[26]	Oikawa et al., 2015[28]	Choudhury et al., 2016[27]
1. Were patient's demographic characteristics clearly described?	Y	Y	Y	N	Y
2. Was the patient's history clearly described and presented as a timeline?	Y	Y	Y	Y	Y
3. Was the current clinical condition of the patient on presentation clearly described?	UC	UC	Y	Y	Y
4. Were diagnostic tests or assessment methods and the results clearly described?	Y	Y	N	N	Y
5. Was the intervention(s) or treatment procedure(s) clearly described?	UC	NA	NA	NA	UC
6. Was the post-intervention clinical condition clearly described?	N	NA	NA	Y	NA
7. Were adverse events (harms) or unanticipated events identified and described?	NA	NA	NA	NA	NA
8. Does the case report provide takeaway lessons?	UC	Y	Y	Y	Y

Captions: Y = yes; N = no; NC = unclear; NA = not applicable

Table 2. Analysis of the risk of bias of cross-sectional observational studies with the Joanna Briggs Institute protocol

	Marchisio et al., 2008[10]	Marchisio et al., 2014[29]	Janek et al., 2016[30]	Jung et al., 2016[9]
1. Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y	Y
2. Were the study subjects and the setting described in detail?	Y	Y	Y	Y
3. Was the exposure measured in a valid and reliable way?	Y	Y	Y	Y
4. Were objective, standard criteria used for measurement of the condition?	Y	Y	Y	Y
5. Were confounding factors identified?	Y	Y	UC	UC
6. Were strategies to deal with confounding factors stated?	Y	Y	N	Y
7. Were the outcomes measured in a valid and reliable way?	Y	Y	Y	Y
8. Was appropriate statistical analysis used?	Y	Y	NA	Y

Captions: Y = yes; N = no; NC = unclear; NA = not applicable

Table 3. Analysis of the risk of bias of case series with the Joanna Briggs Institute protocol

	Kaga et al., 1995[31]	Kim et al., 2008[8]	Sakai et al., 2002[32]
1. Were there clear criteria for inclusion in the case series?	N	N	S
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	S	S	S
3. Were valid methods used for identification of the condition for all participants included in the case series?	S	S	NC
4. Did the case series have consecutive inclusion of participants?	NA	NA	N
5. Did the case series have complete inclusion of participants?	S	S	S
6. Was there clear reporting of the demographics of the participants in the study?	S	NC	S
7. Was there clear reporting of clinical information of the participants?	S	NC	S
8. Were the outcomes or follow up results of cases clearly reported?	S	S	NC
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	NA	NA	NA
10. Was statistical analysis appropriate?	NA	NA	NA

Captions: Y = yes; N = no; NC = unclear; NA = not applicable

In general terms, the case reports presented the subjects' demographic data, timeline history, and clinical condition[24-27]. One of the studies did not present demographic data[28]. The cross-sectional observational studies presented clearly defined sample inclusion criteria, reliably measured exposure, and standardized criteria used to measure the subjects' status[9,10,29,30]. The case series standardly and reliably measured the subjects' data[31,32].

Seven of the 12 articles had been published more than 10 years before[8,10,24-26,31,32], while the other five were more recent, published from 4 to 6 years before[9,27-30]. These findings demonstrate the need for newer studies, as most of the ones on the audiological profile of individuals with CdLS were published more than 10 years ago, and this population is heterogeneous, with little-known auditory system particularities.

Samples sizes ranged from 1[26-28] to 78[30] participants with CdLS; most studies had less than 14 individuals[8,24-28,31,32] (i.e., small samples). Only four articles had samples with more than 30 participants[9,10,29,30]. Altogether, the studies totaled 244 individuals assessed. The small sample size can be explained by the rarity of CdLS (0.5-10 per 100 thousand[3]). Also, affected individuals have difficulties cooperating and their cognitive impairments limit precise and reliable responses in behavioral hearing tests.

The studies evenly recruited participants of both sexes – altogether, the articles had 116 males and 128 females. As for age range, they assessed individuals from 0[9] to 50 years old[30].

Concerning CdLS diagnosis criteria, most authors only used consensual parameters related to the identification of specific phenotypical characteristics of the syndrome[24,25,27,28,31]. Two studies specified the diagnosis based only on genetic tests[10,32], while another two studies used both diagnostic procedures[26,29]. Three studies did not specify the diagnostic criteria they used[8,9,30]. Hence, future studies should include data on the research subjects' genome to characterize the sample and if possible relate the influence of specific genes to the audiological profile.

BAEP[8-10,24-29,31,32] and PTA[8,10,24,27-32], followed by acoustic immittance measures[9,10,24,26,27,29] and OAE[26-28], were the most used clinical resources in the audiological assessment of research subjects. BAEP was used mostly to obtain electrophysiological thresholds and verify hearing loss (nine studies[8,9,24-28,31,32]), while only two studies analyzed brainstem auditory pathway integrity[25,26]. Moreover, two studies did not specify BAEP results[10,29]. Likewise, of the six studies that measured acoustic immittance[9,10,24,26,27,29], only four described the results[9,24,26,27], and of the three studies that analyzed OAE[26-28], only two presented the results[26,28].

The studies included in this review did not demonstrate data on audiometric configuration or which frequencies tested with PTA were the most affected.

It must be pointed out that not all selected articles clearly described the criteria used to classify the types

and degrees of hearing loss, tympanograms, and BAEP reference standards. The studies that described the reference standard followed recommended international criteria, considering as normal the hearing thresholds lower than or equal to 25 dBHL and tympanograms based on criteria presented by Jerger in 1970. However, some information had to be inferred from text reading in some cases.

The few cross-sectional studies, with larger sample sizes, different assessment protocols, and different normal standards made it impossible to conduct a meta-analysis and analysis of the certainty of evidence with GRADE (Grading of Recommendations Assessment, Development, and Evaluation)[33]. Hence, future studies should also present in minute detail the reference standards and procedures used.

Audiological characteristics in CdLS

The analysis of the studies surveyed in this review demonstrates an incidence of hearing loss, identified with PTA and electrophysiological threshold (measured with BAEP), ranging from 60%[8] to 100%[24-28,31,32] of the population assessed in each study. Even though most studies had a small sample size, including case reports[24-28] and case series[31,32], it was evident that most individuals with CdLS had some type of hearing loss, corroborating the syndrome description findings, which state that hearing loss affects about 80% of individuals with CdLS[5].

Conductive hearing loss was the most often type verified with PTA[8,10,24,27-32], corresponding to 49.20% of individuals with CdLS, followed by sensorineural (13.49%) and mixed hearing loss (11.11%). However, three studies did not specify the type of hearing loss (26.19%)[30-32].

Besides the data measured with PTA, cochlear and middle ear impairments were also verified with acoustic immittance measures, OAE, and BAEP.

Regarding acoustic immittance measures, there was a high incidence of type B tympanograms, corresponding to more than 92.85% of individuals with CdLS[9,26,27], although two studies found bilateral type A tympanograms[9,24].

Acoustic reflexes, in their turn, were described in only two of the four articles that measured acoustic immittance. They found one case with bilaterally present acoustic reflexes[24] and one case with bilaterally absent acoustic reflexes, due to middle ear impairment (type B tympanogram)[26].

One of the articles that presented OAE results found absent distortion-product and transient-evoked OAE, due to conductive hearing loss[26]. Another article verified distortion-product OAE present in the right ear, while the responses were absent in the left ear, associated with sensorineural hearing loss[28].

Most studies verified the hearing of individuals with CdLS using BAEP[8-10,24-29,31,32]. However, only two of them reported data on wave latencies[25,26]. One of these described only normal latencies in wave I and interpeak interval I-V[25], while the other described BAEP with increased absolute latencies and normal interpeak intervals, confirming this patient's middle ear impairment[26].

Considering the joint analysis of the different procedures, conductive hearing loss was found most frequently, followed by sensorineural hearing loss. Using different procedures to make up the audiological assessment battery – even though this led to studies with different methodologies, hindering the collection of more concise data in this review – is an often-used clinical resource in clinical routine. Moreover, some procedures cannot be performed on these individuals, because of either their age or intellectual disability.

The greater incidence of conductive hearing loss did not corroborate the data obtained in a study that described the sensorineural hearing loss as the most common impairment, followed by conductive hearing loss[11].

Among the mutations present in this syndrome, a study highlighted the association of conductive hearing loss in individuals with the NIPBL genetic variant (particularly in truncating mutations). However, the authors pointed out that further studies are needed to assess new mutations identified in CdLS, confirm this finding, and define the best means to follow up on the hearing of patients with CdLS [29]. If future studies confirm this hypothesis, it may explain the divergence between the data obtained in this review and the study by Bergeron et al.[11], as none of the studies specified the research subjects' genetic mapping.

The possible conductive hearing loss etiologies in this population include external acoustic meatus stenosis, middle ear ossicular anomalies, nonspecific middle ear anomalies (nonspecific soft tissues filling in the middle ear), and acute or chronic otitis media[11]. Therefore, inserting ventilation tubes is not always a feasible clinical resource to treat these patients' middle ear, as some of them have middle ear malformations beyond the presence of cavity secretion[9]. As

for sensorineural hearing loss etiologies, inner ear anomalies, such as cochlear dysplasia, stand out[11].

Nine studies described the degree of hearing loss, measured with PTA[8,10,24,27-32]. Mild hearing losses predominated (46.82%), followed by moderately severe (23.01%), moderate (11.11%), profound (10.31%), and severe, the least frequent one (4.76%). Furthermore, a study did not specify the degree of hearing loss, corresponding to 3.96% of all cases assessed with PTA[30]. Hence, their degree ranged from mild to profound – the mild ones predominated. These data corroborate the findings in the literature, which verified a similar variation, as about one third of patients had mild hearing loss[11].

BAEP also verified that the electrophysiological threshold ranged from 40 dBnHL[25,27] to absent responses at 100 dBnHL[25,32]. Mild hearing loss was verified in 10% of cases[8], bilateral severe in more than 40% of individuals[31], and profound in 10% of them[8].

However, comparisons demonstrate quite different proportions of degrees of hearing loss between BAEP and PTA – severe hearing losses are more frequent in BAEP and mild ones in PTA. This divergence can be explained by the fact that individuals with more severe CdLS phenotypes usually are not cognitively capable of responding to PTA tasks. Thus, they can only be assessed with other objective measures, which do not depend on the subject's response, like BAEP. Therefore, PTA is used in cases of milder phenotypical expressions, whereas BAEP is the main resource available to diagnose more severe cases of CdLS. Symptoms are consequently more present in these patients, which may impair more auditory system structures.

Hearing loss in this population requires special attention and must not be merely accepted as a change inherent to the disease. Hence, individuals with CdLS must have otorhinolaryngological and speech-language-hearing assessment and follow-up from birth, including routine audiological examinations and strategies to treat hearing loss (e.g., ventilation tubes, drugs, and/or hearing aids). This early care enables hearing loss diagnosis and intervention, positively impacting the development of their language and hearing skills, improving verbal and cognitive development in social and professional settings, as well as the quality of life of individuals with CdLS and their families.

To solve problems caused by hearing loss, it is highly important to have public policy guidelines to address the issue. This requires a battery of diagnostic tests, including behavioral observation assessment, PTA, OAE, BAEP, and acoustic immittance measures. Thus, when any change is detected, treatment (e.g., cochlear implants, hearing aids, and bone-anchored hearing aids) must be readily available to them. After all, according to the literature[11], these devices are, to some extent, successful in people with CdLS.

CONCLUSION

Individuals presented with CdLS have a high incidence of hearing loss, which can range from mild to profound. Middle ear changes are the factor that most influences audiological impairment.

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APPENDIX 1

Databases, sources of information, and search strategies

Databases	Descriptors
Embase https://www.embase.com/#search	('audiology'/exp OR 'hearing impairment'/exp OR 'hearing disorder'/exp) AND 'de lange syndrome'/exp
ISI of Knowledge http://apps.webofknowledge.com	TÓPICO: ((audiolog* OR hearing loss OR deaf* OR hearing disorder*) AND (de lange syndrome))
Lilacs https://lilacs.bvsalud.org/	(audiolog*) OR (hearing loss) OR (deaf*) OR (hearing disorder*) AND (de lange syndrome)
PubMed-Medline http://www.ncbi.nlm.nih.gov/pubmed	(((((audiolog*[Mesh]) OR «hearing loss»[Mesh]) OR deaf*[Mesh])) OR hearing disorder*[Mesh]) AND «de lange syndrome»[Mesh]
SciELO https://scielo.org/	EN: (audiolog$) OR (hearing loss) OR (deaf$) OR (hearing disorder$) AND (de lange syndrome) PT: (audiolog$) OU (perda auditiva) OU (surdez) OU (transtornos da audição) E (Síndrome de Cornélia de Lange)
Scopus https://www.scopus.com/	((audiolog$) OR (hearing loss) OR (deaf$) OR (hearing disorder$) AND (de lange syndrome))
Sources of information	**Descriptors**
Google Scholar https://scholar.google.com.br/?hl=pt	audiology («hearing loss» OR deafness OR «hearing disorders») AND «de lange syndrome»
OpenGrey http://www.opengrey.eu/	«audiolog*» OR «hearing loss» OR «deaf*» OR «hearing disorder*» AND «de lange syndrome»
Proquest https://www.proquest.com/	(((((audiolog*) OR «hearing loss») OR deaf*)) OR hearing disorder*) AND «de lange syndrome»

Captions: EN – English; PT – Portuguese.

APPENDIX 2

Studies excluded after full-text reading and respective reasons for exclusion

Reference	Reason for exclusion
1. Eliason MJ, Melzer JM, Gallagher TQ. Cornelia de Lange syndrome: what every otolaryngologist should know. Ear, Nose & Throat Journal. 2017;96(8):E6-E9.	Not meeting the study objective
2. Hamilton J, Clement WA, Kubba H. Otolaryngological presentations of Cornelia de Lange syndrome. Int. J. Pediatr. Otorhinolaryngol. 2014;78(9):1548-50.	Unspecific methodology
3. Kozlowski J, Wierzba J, Narozny W, Balcerska A, Stankiewicz C, Kuczkowski J. Auditory function in children with Brachmann-de Lange syndrome. Otolaryngol Pol. 2006;60(4):577-81.	Unavailable full text (author contacted)
4. Mariani M, Decimi V, Bettini LR, Maitz S, Gervasini C, Masciadri M et al. Adolescents and adults affected by Cornelia de Lange syndrome: A report of 73 Italian patients. Am J Med Genet C Semin Med Genet. 2016;172(2):206-13.	Unspecific methodology
5. Moore MV. Speech, hearing, and language in de Lange syndrome. J Speech Hearing Dis. 1970;35(1):66-9.	Unspecific methodology
6. Psillas G, Triaridis S, Chatzigiannakidou V, Constantinidis J. Cornelia De Lange syndrome and cochlear implantat.ion. Iran J Otorhinolaryngol. 2018;30(101):369	Not meeting the study objective
7. Pulec JL, Saadat D. Multichannel cochlear implantation in a child with Brachmann-de Lange syndrome. Otolaryngol Head Neck Surg. 1995;113(5):641-3.	Not meeting the study objective
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9. Marres HA, Cremers CW, Jongbloet PH. Hearing levels in the Cornelia de Lange syndrome. A report of seven cases. Int J Pediatr Otorhinolaryngol. 1989;18(1):31-7.	Results not clearly presented

Estudos que foram excluídos após leitura do texto completo e os respectivos motivos de exclusão