

# Current Overview of Blepharocheilodontic Syndrome (BCD). A Systematic Review and Case Report

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## Abstract

Blepharocheilodontic syndrome is a rare autosomal dominant disorder characterized by craniofacial anomalies. Bilateral cleft lip/palate, dental agenesis, and eyelid malformations are usually present in individuals with this condition; however, hypothyroidism or joyful agenesis and imperforate anus frame unusual phenotypic features.

**Objective:** The aim of this systematic review was to create a current overview of blepharocheilodontic syndrome (BCD) through a case report.

**Methods:** It was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with the Prospective Prior International Registry of Systematic Reviews (PROSPERO). Updated scientific data were generally obtained from PubMed, Medline, Embase, Researchgate, Lilacs, Proquest, Google Scholar, Epistemonikos, Springer, ScienceDirect, Scielo, Ovid, Taylor&Francis, Cochrane, Scientific Reports, UNA Discovery Service, Web of Science, Orphanet, ACPA, Dynamed, Dialnet, EBSPCO, and WebMD. The quality of evidence of the included articles was assessed using the Cochrane risk of bias tool.

**Results:** A total of 296 articles were identified after the initial search and 129 duplicate articles were excluded after the first screening. Of the 167 papers screened by title and abstract, 22 met the parameters of the eligibility criteria.

**Conclusions:** It is difficult to establish exact conclusions about CBD syndrome, the genetic origin and the dental and medical care guidelines are still under discussion and hardly detailed in the literature found, so the authors recommend caution in the results and the clinical-therapeutic follow-up of the published cases.

**Keywords:** blepharocheilodontic syndrome; blepharo-cheilo-odontic syndrome; euryblepharon; cleft palatal syndrome; ectropion inferior-cleft lip and/or palate syndrome; BCD syndrome.

## 1.Introduction

Blepharocheilodontic syndrome (BCD) (OMIM 119580) is a rare autosomal-dominant condition characterized by ectodermal defects and craniofacial abnormalities such as bilateral cleft lip and palate, eyelid malformations, and teeth agenesis [1–3]. Since first reported in 1996 by Gorlin and associates [4], only a few confirmed cases have been informed. Ophthalmic features include wide palpebral fissures (euryblepharon), an anterior lamellar shortage of the lower eyelid that commonly reveals the mucosa and contributes to ectropion, and a double row of eyelashes in the upper eyelids [5,6]. When presented together, eyes may not close completely (lagophthalmia) and are usually accompanied of distichiasis and conjunctivitis episodes [7–9]. Eyelid anomalies should be recognized

and surgically corrected to minimize the morbidity of severe ectropion and lagophthalmos [10,11]. Moreover, sparse hair in the temporal region together with the sparsity of eyebrows, eyelashes, nail hypoplasia, and cutaneous abnormalities are important components of ectodermal dysplasia [12,13]. Teeth manifestations include oligodontia, microdontia, and shape malformations that involve both dentitions [1,14]. The sites of missing teeth are usually adjacent to the cleft of the alveolus. (13). In addition, the craniofacial skeletal pattern can be described as Skeletal Class III with hypoplastic maxilla [4]. Rarely reported imperforate anus, neural tube defect, syndactyly, and thyroid malfunction or agenesis are described as phenotypic manifestations of the BCD syndrome [2,15].

Transcription factors including TTF-1, TTF-2 and PAX-8 are involved in the thyroid gland embryogenesis and function, but only 3% of reported thyroid dysgenesis were linked to their mutation [16]. The co-occurrence of imperforate anus can be explained by a defect in the regulation of apoptosis and fusion during the first semester of fetal development [15]. The etiology of cleft lip and palate is multifactorial and may be attributed to genetic and environmental implications [17,18]. Preliminary molecular studies have failed to identify causative mutations in TP63, IRF6, TBX10, FOXE1, and OSR2 comprising the thyroid and palate formation [2]. Freitas, E et al. [3] suggest that unsequenced regions might present pathogenic alterations. To date, studies have identified that the pathogenic genes cadherin 1 (CDH1) and cadherin-6 (CTNND1) are noted as responsible for the BCD syndrome [14]. CDH1 encoding E-cadherin comprise an important role in epithelial cell adherence; involved in eyelid, craniofacial, tooth, and hair development [17,19]. CTNND1 encodes catenin delta 1 (alias p120ctn) an armadillo repeat containing proteins that interact with the juxta-membrane cytoplasmic tail of CDH1 and control the stability of the complex [2]. On the other hand, CDH1 gene variants were identified in multigenerational hereditary diffuse gastric cancer (HDGC; OMIM 137215) and lobular breast cancer (LBC), thus including individuals with non-syndromic cleft lip/palate [5,20]. CDH1 variant carriers have a lifetime risk of developing diffuse gastric cancer and LBC [7,21]. The risk-reducing measures include prophylactic gastrectomy and annual breast magnetic resonance image [22]. Additionally, could be mentioned that BCD syndrome shares clinical similarities with Ectrodactyly-ectodermal dysplasia-cleft syndrome, Hay-Wells syndrome and Van der Woude syndrome / popliteal pterygium syndrome [6]. Therefore, a specific genetic analysis should be carried out on individuals suffering from this panorama.

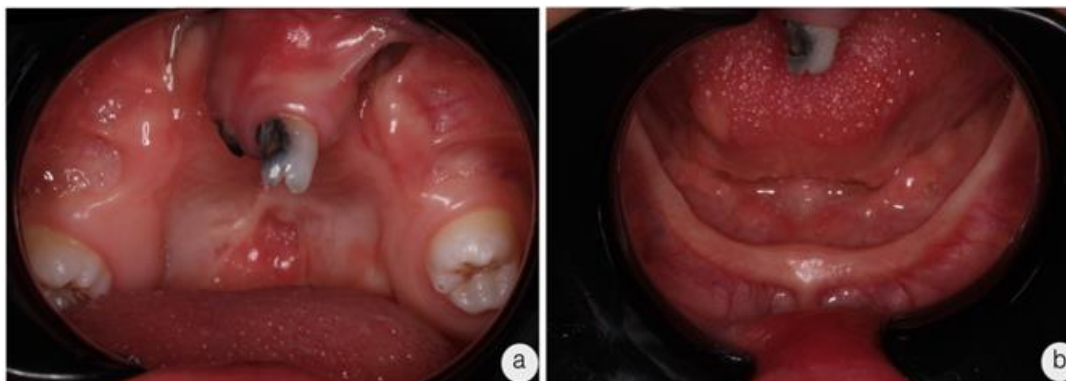
## 2. Case report

An 8-year-old patient attended with her parents to the maxillofacial surgery and orthodontics service of the Catholic University of Cuenca for

outpatient care. The mother stated that she had no prenatal complications and gave birth at term. There was no family history of congenital facial anomalies. After thorough anamnesis, the parents report that the case was reported at 4 years of age; however, the publication is not found in an indexed scientific database, so this publication was not found and could not be part of the content of this systematic review. The ophthalmologic examination was significant for bilateral ectropion of the lower eyelids, lagophthalmos and scarcity of eyelashes and eyebrows, there was no evidence of damage to the pupil, iris or optic nerve, the patient underwent canthoplasty and palatoplasty at 3 years and 5 months of age, reducing the morbidity of ectropion and lagophthalmos, and there were no significant findings regarding hearing, taste, development, anatomy, and function of internal organs. The frontal facial clinical examination showed scars in the infraorbital region, the impossibility of achieving complete closure of the eyelids with exposure of the inner surface of the upper and lower eyelid; likewise, new eyelash growth could be observed from the superficial glands of the eyelids, compatible with distichiasis. In the extraoral region, it was possible to observe a post-cheiloplasty hypertrophic scar of bilateral labial fissure due to the surgical approximation of the labial surfaces in childhood, accompanied by lip incompetence and projection of the chin, it was also evident a concave profile with a difference of middle and lower thirds and a smile without teeth. (Figure 1) The intraoral examination showed oligodontia and malformation of the teeth present in the mouth, bilateral fissure of the maxilla with the presence of nasopalatine fistulas, maxillomandibular hypoplasia with evident post-surgical scarring processes; in addition, a correct position and function of the tongue with interaction of the alveolar ridges and the insertion of the oral frenulae. (Figure 2) According to an orthopantomography performed at the age of 7 years, two conical upper central incisors, four permanent molars and the probable formation of upper and lower second molars were observed, as well as the bilateral fissure of the maxilla accompanied by deviation of the nasal septum and the maxillary segment is anchored to the portion of the right



**Figure 1:** Facial photographs: a) forehead without smile b) forehead with smile c) right lateral without smile d) left lateral with smile e) eye region f) lip region.



**Figure 2:** Intraoral photographs: a) upper occlusal b) lower occlusal.



**Figure 3:** Orthopantomography image.

At that time, the diagnosis of the lateral radiograph revealed a class III skeletal relationship of the maxillofacial cranio-cervico region, due to hypoplasia of the maxilla [23]; likewise, dento-facial and dento-skeletal positions and relationships were limited due to oligodontia. (Figure 4) Subsequently and according to the ALARA (As Low as Reasonably Achievable) criteria, it was decided that a tomographic evaluation was necessary before any clinical-surgical intervention and as a choice of the imaging modality in which to minimize radiation, a CONE BEAM (Cone Beam Computed Tomography) of the head and neck with a scanning time of 18s (emission time of 3.6 s) at 110 kV [25] was chosen. The tomographic reconstruction was performed using BlueSky plan software <https://www.blueskyplan.com/>, which allowed the analysis of the cranio-

cervical maxillofacial relations in which the decrease of airways with cervical rectification, inverted maxillary-mandibular transverse planes (maxilla with transverse underdevelopment), bilateral maxillary fissure with compression and deviation of the septum-nasal; Likewise, it is evident that, contrary to clinical and radiographic evidence, there is an absence of upper and lower alveolar ridges, for this reason it is appropriate to think that the visible clinical ridges are compatible with gingival cushions compensatory to mastication, swallowing and physiological movements of the stomatognathic system; finally at the orbital level, it was possible to observe the age-appropriate growth of the orbit with the naso-maxillary structures. (Figure 5)

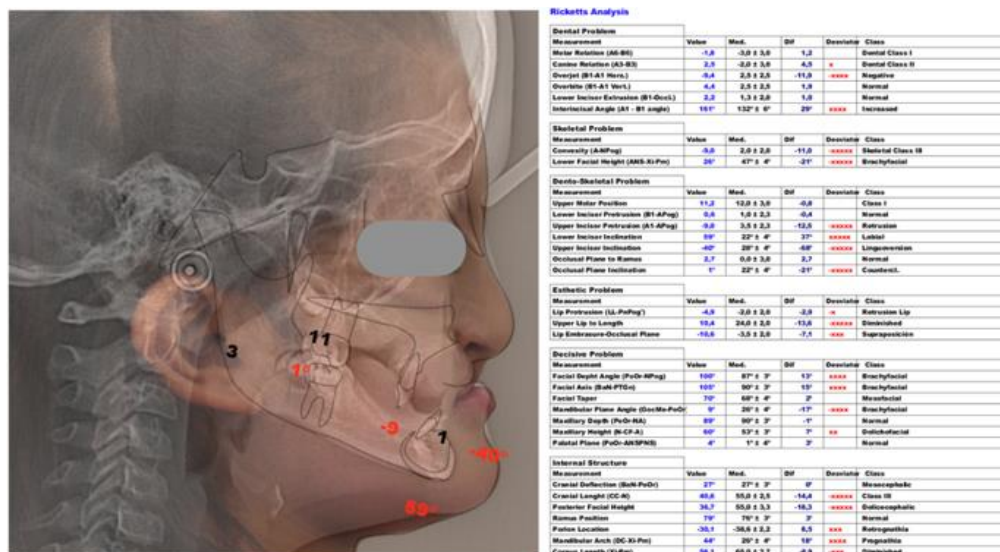


Figure 4: Diagnosis of cephalometric evaluation.

Moreover, the multidisciplinary medical team of the head and neck hospital analyzed the laboratory tests and the genetic mapping in which he was diagnosed as "Blepharochelo-dontic syndrome" accompanied by bilateral acute otitis, lagophthalmos (H022 - CIE 10) caused by bilateral ectropion (H021 - CIE 10) without ocular pathology adjacent to his basic syndrome (normal left optic nerve with a thickness of 3.4mm and normal right optic nerve with a thickness of 3.0mm). The color Doppler analysis showed that the central artery and vein were bilaterally patent; furthermore, a new canthoplasty surgery was not considered necessary since the upper eyelid was slightly adjusted in relation to the lower eyelid, therefore, she was referred to ocular clinical treatment (lenses, lubricant

and periodic control). Likewise, moderate conductive hypoacusis of the left ear is referred and the speech test detected speech difficulties associated with cleft and oligodontia in the primary and permanent dentitions. On the other hand, the dental treatment planning will focus on taking advantage of the stages of growth and cranio-facial development with approximation of the maxillary segments towards mesial, to later continue with the integral dento-maxillo-facial rehabilitation, at the same time, medical appointments were scheduled for follow-up in the services of Otolaryngology, Pediatrics, Genetic Counseling, Psychiatry, Psychology, Early Stimulation, according to the needs of each stage of the patient.

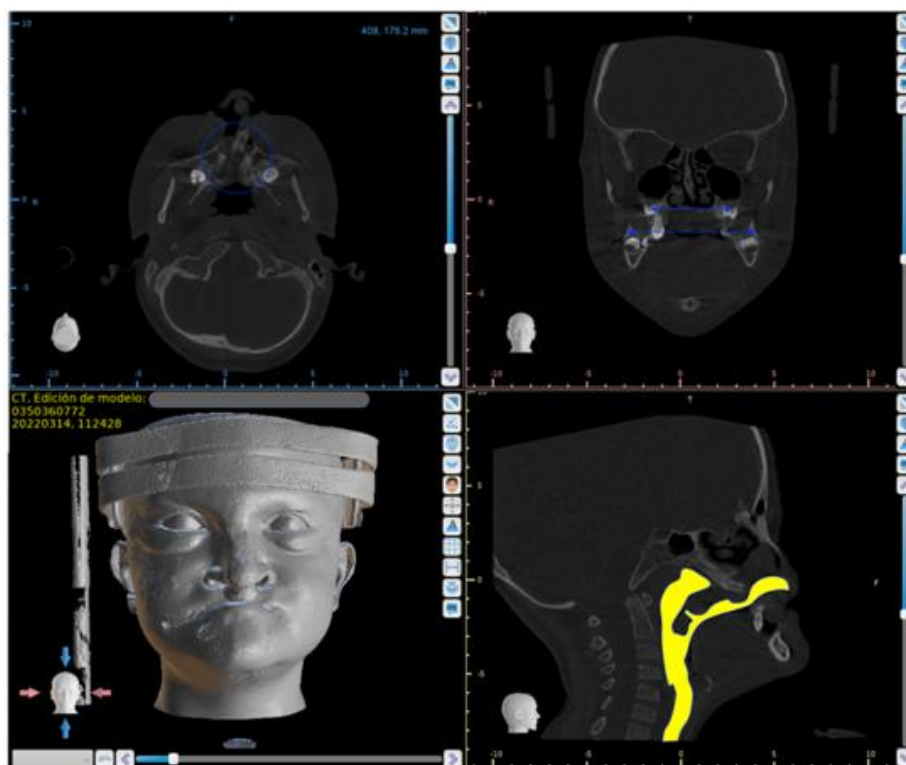


Figure 5: Maxillofacial cranio-cervical CBCT evaluation.

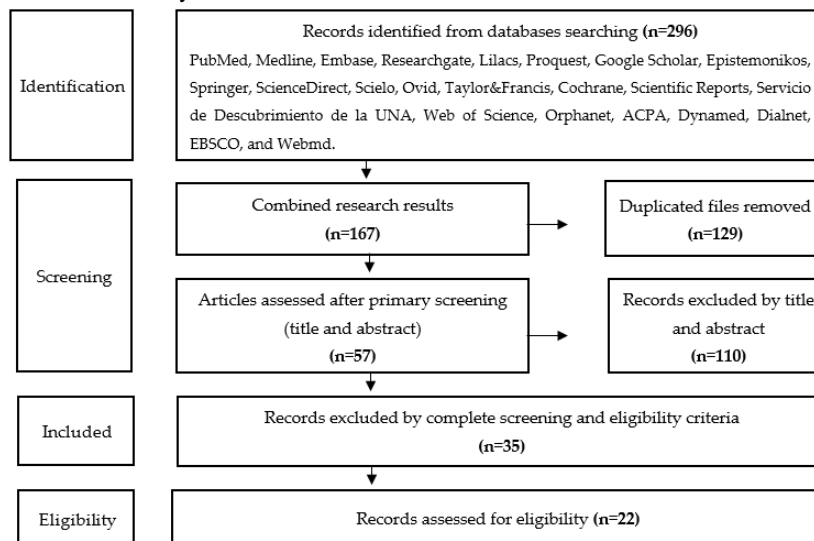
### 3. Materials and Methods

The systematic review considered in its eligibility criteria, observational prospective and retrospective studies, longitudinal and cross-sectional comparative cohorts, systematic reviews, literature reviews, case reports, case series, letters to the editor, and clinical practice guidelines. Exclusion criteria were applied for university degree research documents. The language, publication date, country of precedence, ethnicity, sex and age of the studied population, did not figure out a research limitation. The following navigators and scientific databases were included in the data extraction process: PubMed, Medline, Embase, Researchgate, Lilacs, Proquest, Google Scholar, Epistemonikos, Springer, ScienceDirect, Scielo, Ovid, Taylor&Francis, Cochrane, Scientific Reports, UNA Discovery Service, Web of Science, Orphanet, ACPA, Dynamed, Dialnet, EBSCO, and Webmd, until the established death line, June 10th from 2024. The search strategy was based on the DeCS/MeSH Health Sciences Descriptor terms. Controlled and indexed descriptors were used for each database, being linked by the operators OR and AND. The research guidelines in PubMed included (((((((CDH1) OR (CTNND1)) AND (cleft palatal)) AND (spina bifida)) AND (anal atresia)) AND (tooth agenesis)) AND (thyroid agenesis)) AND (euryblepharon)) AND (lagophthalmia)) AND (blepharon-cheilo-dontic)) OR (blepharocheilodontic). This systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database ID number CRD42023410397 and follows the recommendations established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [24]. The protocol did not figure modifications after initially presented. Although the possibility of carrying out a meta-analysis was proposed, the 22 included studies showed scarce homogeneity in the sample ages and a diverse scientific approach. Despite the methodological rigor employed in the present systematic review, conducting a meta-analysis was not feasible due to intrinsic limitations in the available body of literature on

Blepharocheilodontic Syndrome (BCD). BCD is an ultra-rare genetic disorder with an estimated prevalence of fewer than 1 case per 1,000,000 individuals, resulting in a significant scarcity of large-scale original studies. Most of the existing publications consist of case reports or small case series, exhibiting high heterogeneity in reported clinical features, diagnostic methods, therapeutic interventions, and long-term follow-up. The current studies also show considerable methodological variability, including differences in diagnostic criteria, classification of genetic variants (such as CDH1 and CTNND1 mutations), and the clinical outcomes assessed, thereby precluding adequate data homogenization for quantitative synthesis. Furthermore, the absence of randomized controlled trials, cohort studies, or comparative series limits the possibility of applying meta-analytic techniques using robust statistical models, as a meta-analysis requires design homogeneity, data comparability, and sufficient statistical power to generate valid estimates. For these reasons and following international methodological guidelines such as PRISMA 2020 and the recommendations of the Cochrane Collaboration, in contexts where individual clinical reports predominate, a qualitative systematic review represents the most appropriate approach to synthesize existing knowledge, identify gaps in the literature, and propose future research directions.

### 4. Results

There was a total of 296 titles identified after the initial search, and 129 duplicated articles were excluded after the first screening. Of the 167 documents screened by title and abstract, 22 gathered the eligibility criteria parameters. In each obtained document, the risk of study bias filter was applied, where a BCD syndrome confirmed laboratory genetic exam and specific clinical manifestations were required to be considered for the research. (Figure 6) Data and results from the cited authors were extracted, analyzed, contrasted and compared with the present reported case.



**Figure 6:** Data extraction and analysis procedures.

#### 4.1. Description of Includes Studies

The data extraction process met the criteria and terms detailed in the methodology section. As a result of this meticulous research, 22 selected documents were classified by study style, year and country of origin. (Table 1) The publication date did not figure a limitation for eligibility

criteria, given that updated literature is scarce. The first reported case, dates from 1996 by Gorlin et al. [8] to 2014 when 11 publications in 7 countries reported 18 confirmed BCD syndromic individuals. Nevertheless, these publications emphasized phenotypic characteristics, excluding details related to genetic mutations linked to the syndrome

origin. In 2020, LeBlanc et al. [7] reported a case in Australia. In 2016, a case-control study performed by Awadh et al. [4] analyzed 40 patients with BCD syndrome-related dental and craniofacial features. Nonetheless, comparisons and conclusions were established after identifying only 4 confirmed cases, denoting possible biases. A similar situation occurred with Green et al. [19] research letter that comprised 299 feature-related individuals associated with lobular breast and gastric

cancer risk. Afterward, four original articles written by Ghoumid et al. [20] in 2017, Kievit et al. [5] in 2018, Ben Aissa-Haj et al. [21] and Lin et al. [14] in 2022, addressed generalities about the syndrome. Two literature reviews from Luo et al. [22] and Peng et al. [17] performed in 2020 were included; as well as a correspondence from Ghoumid et al. [20] from 2020, a research report by Green et al. [19] from 2022, and a research letter from Freitas et al. [3] from 2007 met the eligibility guidelines.

Type of Study	Year of Publication	Country of Origin
Case-control studies	2016	Finland
Original Articles	2017, 2018, 2022, 2022	France, Nederland, China, and Tunisia
Systematic review	2018, 2020	United States and China
Research reports	2022	United States
Correspondence	2020	France
Research letter	2007	Brazil
Case reports	1957, 1998, 1999, 2001, 2003, 2004, 2005, 2005, 2010, 2014, 2020	Germany, Brazil, Mexico

**Table 1:** Data extraction results classified by style of text, publication year and country of precedence.

## 4.2. Findings

The extracted studies included 20 reported cases, where 12 were male and 8 females. Brazil frames as the country with the greatest prevalence with 7 reported cases of BCD syndrome, followed by Australia and Mexico with 2 reported cases each. Although some studies describe both normal

intelligence and development, ophthalmic features and cleft are the most noticeable phenotypic characteristics. According to the findings, only 2 individuals noted hypothyroidism and thyroid gland agenesis; similarly, ectodermal defects such as hypoplastic nails and sparse hair were barely identified in 2 people. Thus, the phenotypic characteristics of the reported cases are noted in Figure 7

N.-	#1	#2				#3		#4	#5		#6	#7	#8	#9	#10	#11	#12		TO TA L
Author	Gorlin, J. and Wiedemann, H.	Guion-Almeida, M. et al.				Valdéz-de la Torre, M. et al.		Ye n, T. et al.	Gil da Silva, V. et al.		Miyamoto, J. et al.	Martinhago, C. and Ramos, S et al.	Winship, I. and Aftimos, S.	Akihiko, I. et al.	Weaver, N. et al.	Aba bneh, F. et al.	LeBlanc, S. et al.		
Publication Date	1957	1998				1999		2001	2003		2003	2004	2005	2005	2010	2020	2020		12
Country	Germany	Brazil				Mexico		USA	Brazil		Japan	Brazil	New Zealand	Japan	USA	Saudi Arabia	Australia		8
Gender	M	F	F	M	M	M	M	M	M	F	F	F	F	M	M	M	M	F	12 M / 6 F
Age	5 months	5 years	5 years	20 years	17 months	6 years	2 months	3 months	11 months	15 months	3 months	2 months	3 years	14 days	1,5 months	20 months	33 years	6 years	14 days / 33 years
Normal Development					✱				✱	✱		✱	✱						5
Normal Intelligence		✱	✱	✱				✱											4

Prominent Forehead			*		*		*		*		*	*			*			7
Low Ear Set								*	*						*			3
High Front Hair			*		*		*				*							4
Sparse Hair						*		*				*	*		*			5
Sparse Eyebrows				*							*	*			*			4
Abundant Eyelashes		*	*						*	*								4
Sparse Eyelashes						*						*						2
Distichiasis						*		*					*		*			4
Ectropion	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	15
Euryblepharon	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	15
Lagophthalmia	*	*	*	*	*	*	*	*	*	*	*	*				*		13
Hypertelorism	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	13
Bilateral Cleft Lip and Palate	*	*	*	*	*	*	*		*			*				*	*	12
Unilateral Cleft Lip and Palate							*		*	*		*		*				5
Hipodontia in Permanent Dentition		*		*														2
Oligodontia in Temporary Dentition			*		*			*	*		*		*		*		*	8
Oligodontia in Permanent Dentition								*		*						*	*	4

Conical Shaped Teeth		*		*				*			*	*	*					6
Hypothyroidism								*		*								2
Thyroid Agenesis										*					*			2
Nevus											*	*						2
Dermoid Cyst			*								*	*						3
Hypoplastic Nails											*				*			2
Imperforate Anus								*	*					*	*			4
Relative s with BCD Syndrome			*	*			*						*			*	*	6
Relative s with Common Signs of BCD Syndrome, but not suffering it					*										*	*		3

**Figure 7:** Clinical characteristics found in historical reported cases.

## 5. Discussion

LeBlanc et al. described Blepharocheilodontic syndrome as an autosomal dominant condition characterized by cleft lip and palate, oligodontia and ophthalmic abnormalities [7] in 1996. Nevertheless, Weaver et al. [15] and Martinhago and Ramos [16] reported imperforated anus and thyroid gland agenesis respectively, as related manifestations of this ectodermal dysplasia. Ophthalmic features commonly associated with BCD syndrome are variable. Guion-Almeida et al. [18] described four Brazilian patients comprising euryblepharon, lagophthalmia and ectropion of lower eyelids; while Winship & Aftimos [12], and Akihiko et al. [13] reported cases, did not include lagophthalmia. On the other hand, our patient's ophthalmologic diagnosis resulted in bilateral ectropion of lower eyelids and lagophthalmia. Gil da Silva et al. [6] found an enhanced distance between the eyes (hypertelorism) in two individuals, but this characteristic was not appreciated in the current case report. Lip and palate cleft usually presents bilaterally in patients with BCD syndrome [1,7,9], but can also appear unilaterally as reported by Yen et al. [10] and Miyamoto et al. [11]. In addition, Winship & Aftimos [12] described an individual with palatal cleft with no lip or face casualties. Furthermore, oligodontia in both temporary and permanent dentition, and anterior teeth malformations, are greatly noted in reported cases by Akihikos et al. [13]

and Gil da Silva et al. [6] respectively. In contrast, our patient presented a conical shaped incisors and oligodontia in both dentitions. Despite the methodological rigor employed in the present systematic review, conducting a meta-analysis was not feasible due to inherent limitations in the available literature on Blepharocheilodontic Syndrome (BCD). BCD is an ultra-rare genetic condition, with an estimated prevalence of fewer than 1 in 1,000,000 individuals [4], which has led to a significant scarcity of large-scale original studies. Most of the available publications consisted of case reports or small case series, exhibiting high heterogeneity in reported clinical features, diagnostic methods, therapeutic interventions, and long-term follow-up [17]. Furthermore, the existing studies exhibited considerable methodological variability, including differences in applied diagnostic criteria, classification of genetic variants (particularly CDH1 or CTNND1 mutations), and the clinical outcomes assessed, which prevented adequate data homogenization for quantitative integration [18]. Additionally, the absence of controlled clinical trials, cohort studies, or comparative series limited the application of meta-analytic techniques using robust statistical models, as meta-analysis requires design homogeneity, data comparability, and sufficient statistical power to yield valid estimates [24]. These methodological constraints were consistent with those

reported in systematic reviews of ultra-rare diseases, where non-standardized individual publications predominated. Therefore, in accordance with international methodological guidelines such as PRISMA 2020 and the Cochrane Collaboration recommendations, a qualitative systematic review constituted the most appropriate approach to synthesize the available knowledge, identify gaps in the literature, and guide future research directions [25].

## 6. Conclusions

Blepharocheilodontic Syndrome (BCD) is a rare genetic disease mainly associated with mutations in the CDH1 and CTNND1 genes, which impacts craniofacial and dental development. Worldwide, its exact prevalence is uncertain due to the limited number of reported cases, which underlines its rarity and the need to strengthen epidemiological surveillance systems.

Advances in genetic sequencing have allowed a more precise identification of the responsible mutations, facilitating early diagnosis and differentiation with other syndromic conditions; thus, international standards of management protocols recommend a comprehensive evaluation from birth, with longitudinal follow-up to address the functional and esthetic complications of the syndrome; however, guidelines for its clinical management are scarce, with protocols that vary between regions according to available resources. Thus, international standards for management protocols recommend a comprehensive evaluation from birth, with longitudinal follow-up to address the functional and aesthetic complications of the syndrome. At present, specialized centers integrating genetics, pediatrics, internal medicine, surgery, general dentistry and orthodontics have proven to be essential to optimize successful outcomes, although access remains uneven. In addition, therapeutic procedures are predominantly individualized and focus on a multidisciplinary approach that includes reconstructive surgery, systemic management, oral treatment, ophthalmologic treatment and psychological care. However, significant challenges remain in standardizing protocols and generating robust data to strengthen global knowledge and improve the quality of life of affected patients.

**Author Contributions:** Conceptualization, Ronald Roosevelt Ramos-Montiel and Santiago Jose Reinoso-Quezada; methodology, Ronald Roosevelt Ramos-Montiel, Santiago Jose Reinoso-Quezada, and Andrea Susana Astudillo-Carrera; software, Carlos Fernando Andrade Tacuri; validation, Ronald Roosevelt Ramos-Montiel, Paola Patricia Orellana Bravo, and Carlos Fernando Andrade Tacuri; formal analysis, Carlos Fernando Andrade Tacuri and Paola Patricia Orellana Bravo; investigation, Ronald Roosevelt Ramos-Montiel, Santiago Jose Reinoso-Quezada, Andrea Susana Astudillo-Carrera, and Hugo Xavier Guamán-Roldán; resources, Cristian Xavier Astudillo-Carrera and Paola Patricia Orellana Bravo; data curation, Estefanía Raquel Rodríguez-Sanmartín and David Alberto Delgado-Acosta; writing—original draft preparation, Ronald Roosevelt Ramos-Montiel and Andrea Susana Astudillo-Carrera; writing—review and editing, Ronald Roosevelt Ramos-Montiel, Santiago Jose Reinoso-Quezada, and Cristian Xavier Astudillo-Carrera; visualization, Estefanía Raquel Rodríguez-Sanmartín and Fernanda Gabriela Carmona-Barreto; supervision, Ronald Roosevelt Ramos-Montiel; project administration, Ronald Roosevelt Ramos-Montiel; funding acquisition, Ronald Roosevelt Ramos-Montiel and Carlos Fernando Andrade Tacuri. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee for Research in Human Beings of the Universidad Católica de Cuenca (CEISH-UCACUE) reviewed the protocol titled "General Current Description of Blepharocheilodontic Syndrome (BCD): Case Report and Systematic Review" (protocol code CEISH-UCACUE-2024-092). Following the review, the committee determined that the project qualifies as exempt from ethical evaluation according to current legal regulations. This exemption was officially communicated on May 22, 2024, in Cuenca, Ecuador.

**Informed Consent Statement:** Patient consent was waived as the Ethics Committee for Research in Human Beings of the Universidad Católica de Cuenca (CEISH-UCACUE) determined the study, titled "General Current Description of Blepharocheilodontic Syndrome (BCD): Case Report and Systematic Review" (protocol code CEISH-UCACUE-2024-092), to be exempt from ethical evaluation under current legal regulations. Written informed consent for publication was obtained from the patient to ensure compliance with ethical standards.

**Data Availability Statement:** The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. The protocol for this systematic review has been registered with PROSPERO under registration number CRD42023410397. Due to privacy and ethical restrictions, the data supporting the findings of this study are not publicly available."

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**Conflicts of Interest:** The authors declare no conflicts of interest related to this research. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

## Abbreviations

The following abbreviations are used in this manuscript:

**BCD** Blepharo-cheilo-dontic syndrome

**PRISMA** Preferred Reporting Items for Systematic reviews and Meta-Analyses

**PROSPERO** International prospective register of systematic reviews

**PubMed** National Library of Medicine's

**Medline** National Library of Medicine's

**Embase** Excerpta Medica Database

**Lilacs** Literatura Latinoamericana y del Caribe en Ciencias de la Salud

**Scielo** Scientific Electronic Library Online

**Ovit** Interface range of databases, e-journals and e-books.

**ACPA** American Cleft Palate Craniofacial Association

**OMIM 119580** Blepharochelodontic syndrome

**TTF-1** Thyroid transcription factor TTF-1

**TTF-2** Thyroid transcription factor TTF-2

**PAX-8** member of the paired box gene (PAX)

**TP63** Tumor protein p63

**IRF6** Interferon regulatory factor 6

**TBX10** T-box transcription factor 10

**FOXE1** Forkhead box E1

**OSR2** Odd-skipped related transcription factor 2

**CDH1** Cadherin 1

**CTNND1** Catenin delta 1

**LBC** Lobular breast cancer

**DeCS** Descriptores en Ciencias de la Salud

**MeSH** Medical Subject Headings

**ALARA** As Low as Reasonably Achievable

**CONE BEAM** Cone Beam Computed Tomography

**CEISH-UCACUE** Comité de Ética de Investigación en Seres Humanos de la Universidad Católica de

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