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Clinical and radiographic characteristics of pycnodysostosis: A systematic review

Amanda Katarinny Goes Gonzaga[1], Carla Samily de Oliveira Costa[1], Hannah Gil de Farias Morais[1,*], Braz da Fonseca Neto[1], Leão Pereira Pinto[1], Wagner Ranier Maciel Dantas[1], Patricia Teixeira de Oliveira[1], Daniela Pita de Melo[2]

[1]*Postgraduate Program in Dental Sciences, Department of Dentistry, Federal University of Rio Grande do Norte, Natal, Brazil*
[2]*Graduate Program in Dentistry, Department of Dentistry, State University of Paraíba, Campina Grande, PB, Brazil*

ABSTRACT

Purpose: Pycnodysostosis (PYCD), an autosomal recessive syndrome, is characterized by an imbalance in bone remodeling that produces various clinical and radiographic craniofacial manifestations. This review represents a systematic examination of these manifestations, as well as oral features associated with PYCD.

Materials and Methods: A systematic review was conducted across 8 databases from February to March 2023. The search strategy focused on studies reporting cases of PYCD that examined the clinical and radiographic craniofacial and oral characteristics associated with this syndrome.

Results: The review included 84 studies, encompassing a total of 179 cases of PYCD. More than half of the patients were female (55.3%), and the mean age was 14.7 years. Parental consanguinity was reported in 51.4% of the cases. The most common craniofacial clinical manifestation was a prominent nose, observed in 57.5% of cases. Radiographically, the most frequently reported craniofacial characteristics included the presence of an obtuse mandibular angle (84.3%) and frontal cranial bosses (82.1%). Clinical and radiographic examinations revealed oral alterations, with micrognathia present in 62.6% of patients and malocclusion in 59.2%. Among dental anomalies, tooth agenesis was the most commonly reported, affecting 15.6% of patients.

Conclusion: Understanding the clinical and radiographic craniofacial features of PYCD is crucial for dental professionals. This knowledge enables these clinicians to devise effective treatment plans and improve patient quality of life. ***(Imaging Sci Dent 2024; 54: 13-24)***

KEY WORDS: Pycnodysostosis; Maxillofacial Abnormalities; Diagnostic Imaging; Syndrome

Introduction

Pycnodysostosis (PYCD), also known as Toulouse-Lautrec syndrome, was first reported as a distinct condition by Maroteaux and Lamy in 1965. This rare autosomal recessive disorder is characterized by osteosclerotic dysplasia of the skeleton. PYCD arises from the mutation of the gene that encodes the enzyme cathepsin K, which is located on chromosome 1q21. This leads to a reduction in the enzyme's activity.[1,2] As a consequence of this enzymatic deficiency, individuals with PYCD have bones that are abnormally dense and brittle due to impaired bone remodeling processes.[3]

Parental consanguinity is found in approximately 30% of patients diagnosed with PYCD, which has an estimated incidence of 1.7 cases per 1 million births. While it is typically identified at an early age, diagnosis can sometimes be delayed. In those cases, the condition may be detected based on a propensity for bone fractures and infections, which are consequences of increased bone density and compromised bone vascularization.[3,4]

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*Correspondence to : Prof. Hannah Gil de Farias Morais
Department of Dentistry, Federal University of Rio Grande do Norte, Av. Salgado Filho, 1787, Lagoa Nova - Natal / RN, Brazil
Tel) 55-84-32154138, E-mail) hannah_gil@hotmail.com

Common clinical features of PYCD include short stature, prominent nose, acroosteolysis of the distal phalanges, bluish sclera, and hypoplasia of the midface. Additionally, reports frequently indicate craniofacial radiographic findings, such as delayed cranial suture closure, open fontanelles, lack of pneumatization in facial sinuses, and the presence of frontal and parietal bosses.[4,5] Moreover, due to impaired bone remodeling, patients with PYCD face an elevated risk of pathological fracture during dental procedures. This can lead to osteomyelitis, considered the most serious oral complication associated with this syndrome.[4-6] Several oral characteristics are also important to note in the diagnosis and management of PYCD, including maxillary atresia, obtuse mandibular angle, enamel hypoplasia, hypercementosis, malocclusion, delayed eruption, anodontia, narrow and grooved palate, and ectopic teeth.[5]

Although the understanding of PYCD and genetic testing for this condition have advanced considerably, diagnosis is still based primarily on clinical and radiographic characteristics.[7] Consequently, this systematic review was conducted to evaluate and discuss the predominant clinical and radiographic craniofacial and oral features of PYCD. This approach was designed to elucidate the patient profile associated with PYCD and facilitate early diagnosis.

Materials and Methods

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (https://www.crd.york.ac.uk/prospero/), under the protocol number CRD42023398001. This paper was composed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8]

The search terms were developed using the PICO methodology (representing the participants, intervention, control intervention, and outcome measures), which guided the formulation of the following research question: "What are the most common clinical and radiographic craniofacial and oral alterations in patients diagnosed with PYCD?"

An electronic literature search, without time or language restrictions, was performed from February to March 2023 across the following databases: PubMed/Medline, Web of Science, Science Direct, Scopus, Embase, and the Cochrane Collaboration Library. Additionally, OpenGrey and Google Scholar were utilized to explore the gray literature. Manual searches were also performed by cross-referencing the bibliographies of the identified articles. The search strategy employed a combination of the following keywords: pycnodysostosis OR pyknodysostosis OR Toulouse-Lautrec syndrome.

Eligibility criteria and study selection

All published studies that documented cases of patients diagnosed with PYCD and provided descriptions of craniofacial and oral clinical and radiographic characteristics were considered eligible. This included cohort studies, case-control studies, cross-sectional studies, case series, and case reports.

The exclusion criteria for the study were as follows: *in vivo* and *in vitro* studies, review articles, and letters to the editor, except when publications of these types reported cases with sufficient information to confirm a diagnosis of PYCD; and articles for which the full text was unavailable and could not be procured through other means.

Titles and abstracts of all papers identified through electronic searches were independently reviewed by 3 authors (AKGG, CSOC, and HGFM) who had undergone prior calibration. Papers unrelated to the topic of the study were excluded. Following the removal of duplicates, the remaining papers were read in full by the same 3 authors. These reviewers conducted a detailed evaluation of the clinical and radiographic craniofacial and oral characteristics associated with PYCD.

Data extraction and analysis

The papers eligible for data extraction underwent independent assessment. In cases of disagreement, the 3 reviewers engaged in discussion to reach a consensus. From each study, the following data points were collected: the names of the authors, year of publication, country of publication, and age and sex of the patient(s). Additionally, data were obtained regarding general and craniofacial characteristics associated with PYCD, namely consanguinity, affected family members, short stature, brachydactyly, the presence of apnea or snoring, midface hypoplasia, cranial bosses, bluish sclera, exophthalmos, prominent nose, acroosteolysis, increased bone density, open cranial sutures, open fontanelles, craniosynostosis, hypoplastic paranasal sinuses, obtuse mandibular angle, widening of the condyle and coronoid process, fractures of craniofacial bones, malocclusion, micrognathia, dental crowding, narrow and furrowed palate, dental anomalies, osseous sclerosis of the jaw bones, and osteomyelitis in maxillary bones.

The methodological quality of the included papers was assessed according to the CARE guidelines for case reports, a qualitative checklist for observational studies and case reports.[9]

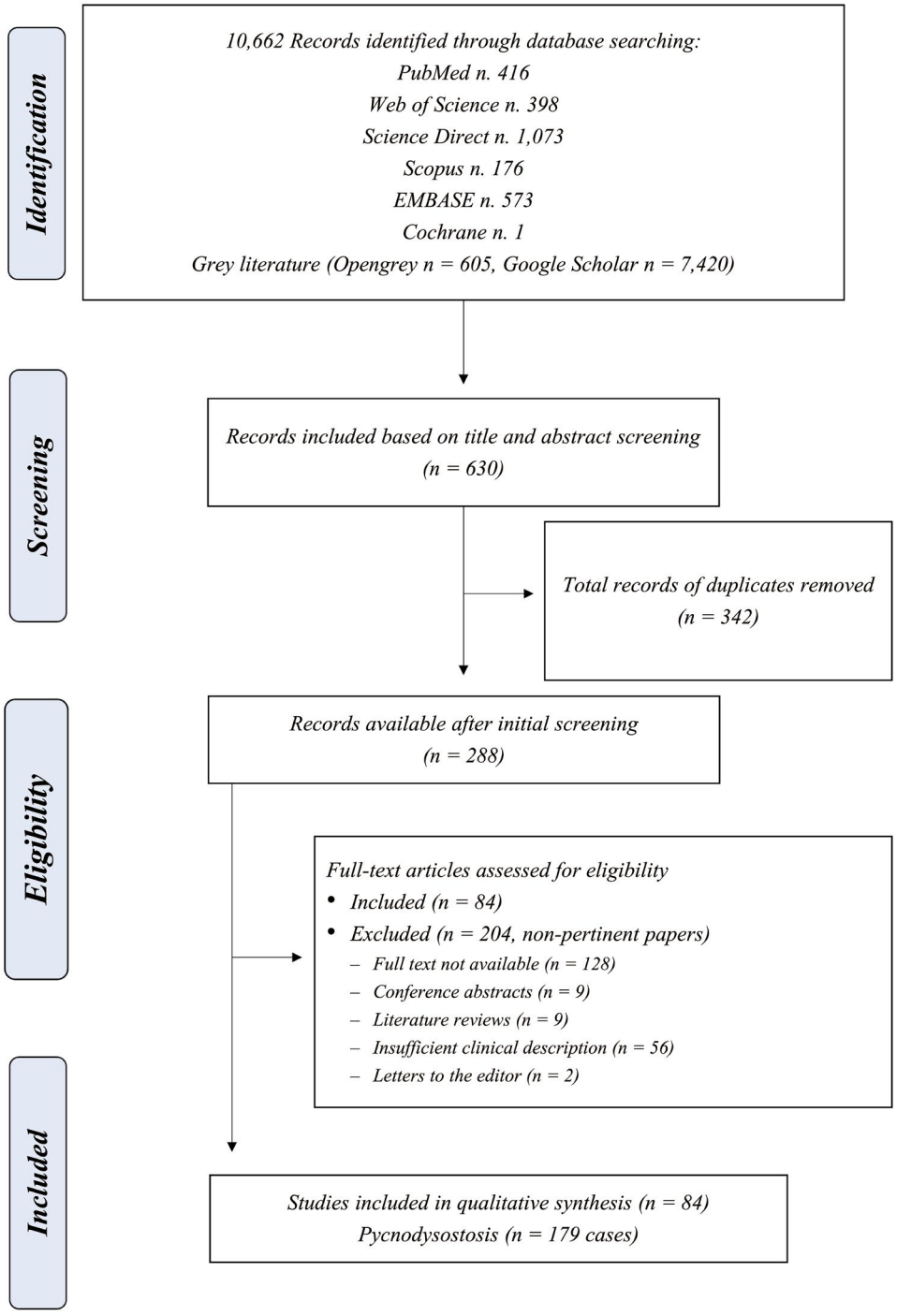

Fig. 1. Flowchart illustrates the article selection process.

Results

Selected studies

The search strategies, which included various database inquiries and manual searches, yielded a total of 10,662 papers. Upon reviewing the titles and abstracts, 288 papers appeared potentially eligible and were read in full by the 3 reviewers (AKGG, CSOC, and HGFM).

Based on examination of the full texts of these papers, 84 studies[3-5,10-90] satisfied all inclusion criteria and were selected for the present systematic review. Overall, the review encompassed 179 clinical cases diagnosed as PYCD. A flowchart detailing the process of article selection is presented in Fig. 1.

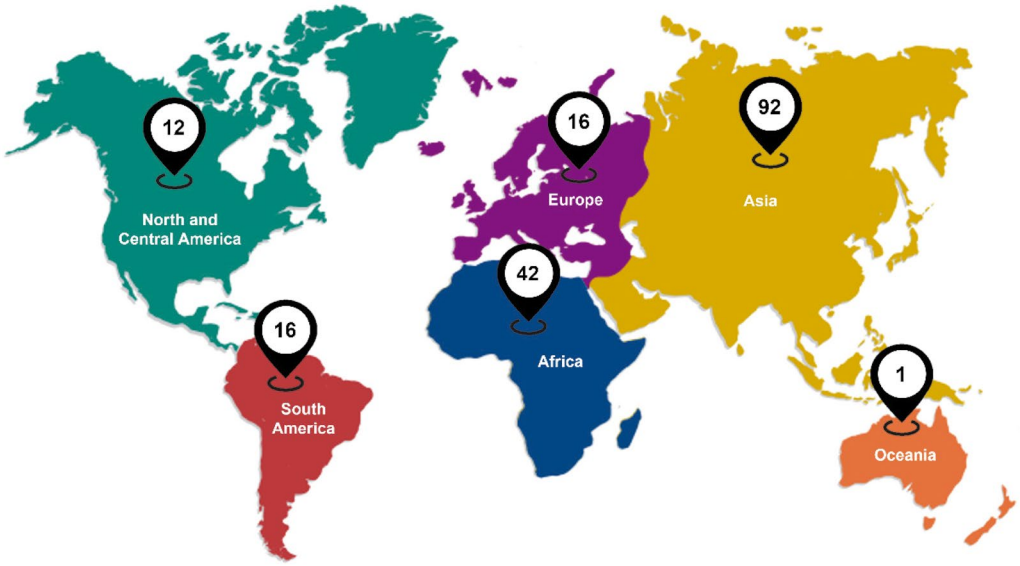

Fig. 2. Geographic distribution, by continent, of pycnodysostosis cases reported in the literature and included in this study.

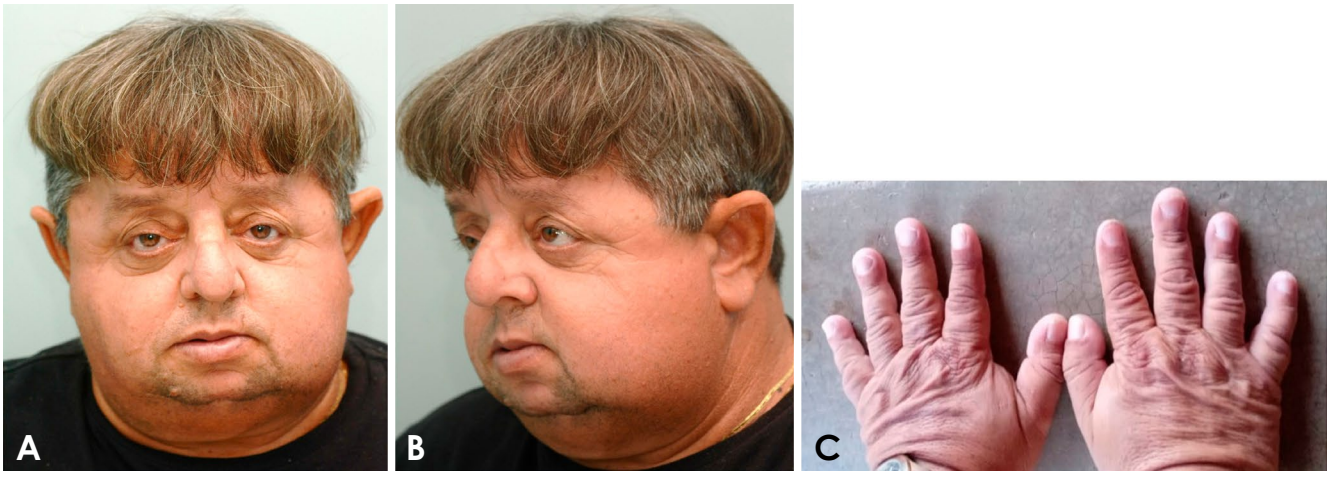

Fig. 3. Frontal extraoral photograph (A) and profile extraoral photograph (B) of a patient diagnosed with pycnodysostosis, present with a prominent nose, micrognathia, retrognathia, hypoplasia of the middle third of the face, and brachydactyly (C).

Clinical and demographic characteristics of patients with PYCD

The demographic analysis of reported PYCD cases revealed that India had the highest number of diagnosed and reported instances (57 cases), followed by Egypt (34 cases) and Brazil (15 cases). Fig. 2 illustrates the geographic distribution of PYCD cases included in this systematic review.

Most patients diagnosed with PYCD were female (55.3%). The mean participant age fell within the second decade of life (14.7 years), with reported ages ranging from 4 months[13] to 58 years.[3] Consanguinity was frequently reported (51.4%), with 26.2% of cases having at least 1 additional family member affected by PYCD. Common clinical features included short stature (found in 86.1% of cases), brachydactyly (66%), and acroosteolysis (58.1%).

Prominent nose (characterizing 57.5% of cases), exophthalmos (49.2%), and hypoplasia of the middle third of the face (47%) emerged as the most frequently observed craniofacial clinical characteristics of PYCD. The clinical and epidemiological details of all PYCD cases included in this study can be found in Tables 1 and 2, as well as in Fig. 3. The study was registered with and approved by the Research Ethics Committee of the Federal University of Rio Grande do Norte, with this approval documented under opinion number 5,926,256.

Table 1. Demographic and general clinical characteristics of cases included in the systematic review

Variable	Number (%)
Sex	
Female	99 (55.3%)
Male	79 (44.1%)
No information	1 (0.6%)
Age	14.7 years (0.2-58 years)
Consanguinity	
Yes	92 (51.4%)
No	36 (20.1%)
No information	51 (28.5%)
Affected family member	
Yes	47 (26.2%)
No	37 (20.7%)
No information	95 (53.1%)
Short stature	
Yes	154 (86.1%)
No	4 (2.2%)
No information	21 (11.7%)
Brachydactyly	
Yes	118 (66.0%)
No	4 (2.2%)
No information	57 (31.8%)
Acroosteolysis	
Yes	104 (58.1%)
No	8 (4.5%)
No information	67 (37.4%)
Apnea/Snoring	
Yes	24 (13.5%)
No	16 (8.9%)
No information	139 (77.6%)

Table 2. Craniofacial clinical characteristics of cases included in the systematic review

Variable	Number (%)
Hypoplasia of middle third of face	
Yes	84 (47.0%)
No	19 (10.6%)
No information	76 (42.4%)
Bluish sclera	
Yes	42 (23.5%)
No	0 (0.0%)
No information	137 (76.5%)
Exophthalmos	
Yes	88 (49.2%)
No	19 (10.6%)
No information	72 (40.2%)
Prominent nose	
Yes	103 (57.5%)
No	20 (11.2%)
No information	56 (31.3%)

Clinical and radiographic craniofacial and oral characteristics of PYCD

In this systematic review, the radiographic craniofacial characteristics most frequently observed were obtuse mandibular angle (84.3%), frontal cranial bosses (82.1%), open fontanelles (67.1%), open cranial sutures (53.6%), and increased bone density in the craniofacial bones (53.4%).

In patients with PYCD, clinical and radiographic information revealed a range of oral alterations. Micrognathia (present in 62.6% of cases), malocclusion (59.2%), dental crowding (54.2%), and narrow and grooved palate (54.2%) were the most frequently observed changes. Additionally, dental anomalies were frequently reported, the most common of which were tooth agenesis (in 15.6% of cases), impacted teeth (14.5%), delayed eruption (12.3%), and enamel hypoplasia (11.7%). The clinical and radiographic craniofacial and oral findings in the evaluated PYCD cases are detailed in full in Tables 3 and 4 and illustrated in Figs. 4 and 5.

Quality assessment of papers included in the systematic review

The results of the quality assessment of the selected studies are presented in Table 5.

Discussion

Craniofacial alterations are frequently observed in individuals with PYCD, an autosomal recessive syndrome. This condition involves the mutation of the gene that codes for cathepsin K, leading to an imbalance in the bone remodeling process.[2,72] According to the present findings, PYCD is relatively prevalent in Asia, with the highest rates observed in India, Egypt, and Brazil. These findings align with those reported by Moreira Júnior et al.[5]

Previous research has underscored the high rate of consanguinity among the parents of individuals diagnosed with PYCD, consistent with the autosomal recessive inheritance pattern of the disease.[4,13,37,49,72,87]

According to Sayed Amr et al.,[13] patients with PYCD typically seek medical attention for concerns such as short stature or unusual bone fractures. In this review, short stature was frequently observed as a clinical feature in the analyzed reports, occurring in 86.1% of cases. Additionally,

Table 3. Radiographic craniofacial characteristics of cases included in the systematic review

Variable	Number (%)
Cranial bosses	
Frontal	147 (82.1%)
Parietal	32 (17.9%)
Occipital	27 (15.0%)
Increased bone density	
Yes	101 (56.4%)
No	1 (0.6%)
No information	77 (43.0%)
Open cranial sutures	
Yes	96 (53.6%)
No	15 (8.4%)
No information	68 (38.0%)
Open fontanelles	
Yes	120 (67.1%)
No	26 (14.5%)
No information	33 (18.4%)
Craniosynostosis	
Yes	24 (13.4%)
No	2 (1.1%)
No information	153 (85.5%)
Hypoplastic paranasal sinuses	
Yes	33 (18.4%)
No	2 (1.1%)
No information	144 (80.5%)
Obtuse mandibular angle	
Yes	151 (84.3%)
No	3 (1.7%)
No information	25 (14.0%)
Enlargement of the condyle and coronoid process	
Yes	12 (6.7%)
No	0 (0.0%)
No information	167 (93.3%)
Fractures of craniofacial bones	
Yes	7 (4.0%)
No	44 (24.6%)
No information	128 (71.4%)

Table 4. Clinical and radiographic oral characteristics of cases included in the systematic review

Variables	Number (%)
Malocclusion	
Yes	106 (59.2%)
No	5 (2.8%)
No information	68 (38.0%)
Micrognathia	
Yes	112 (62.6%)
No	10 (5.6%)
No information	57 (31.8%)
Tooth crowding	
Yes	97 (54.2%)
No	17 (9.5%)
No information	65 (36.3%)
Narrow, grooved palate	
Yes	97 (54.2%)
No	13 (7.3%)
No information	69 (38.5%)
Dental anomalies	
Impacted teeth	26 (14.5%)
Tooth agenesis	28 (15.6%)
Supernumerary	9 (5.0%)
Delay in eruption	22 (12.3%)
Enamel hypoplasia	21 (11.7%)
Root dilaceration	8 (4.5%)
Hypercementosis	7 (4.0%)
Microdontia	4 (2.2%)
Dens-in-dent	2 (1.1%)
Cone tooth	2 (1.1%)
Osseous sclerosis of the maxillary bones	
Yes	11 (6.1%)
No	11 (6.1%)
No information	157 (87.8%)
Osteomyelitis in jaw bones	
Yes	13 (7.3%)
No	6 (3.3%)
No information	160 (89.4%)

brachydactyly was present in 66.0% of cases, and acroosteolysis was noted in 58.1%. While previous studies[10,13,17,31,50] have identified sleep apnea among characteristics of PYCD, it was not commonly observed in this systematic review, appearing in only 13.5% of the reported cases.

The diagnosis of PYCD primarily relies on clinical and radiographic features, as genetic testing is inaccessible through many health services.[4,7] The present systematic review enabled the identification of common craniofacial clinical manifestations in patients with PYCD, including midfacial hypoplasia, blue sclera, exophthalmos, and prominent nose. These distinguishing features are crucial for diagnosing the condition, particularly because clinical diagnosis is essential when complex, specific, and expensive genetic tests are not available to patients with limited financial resources.

According to Schmidt et al.,[72] plain radiographs - including those of the skull, hips, femurs, hands, and feet - interpreted by an experienced radiologist are frequently ade-

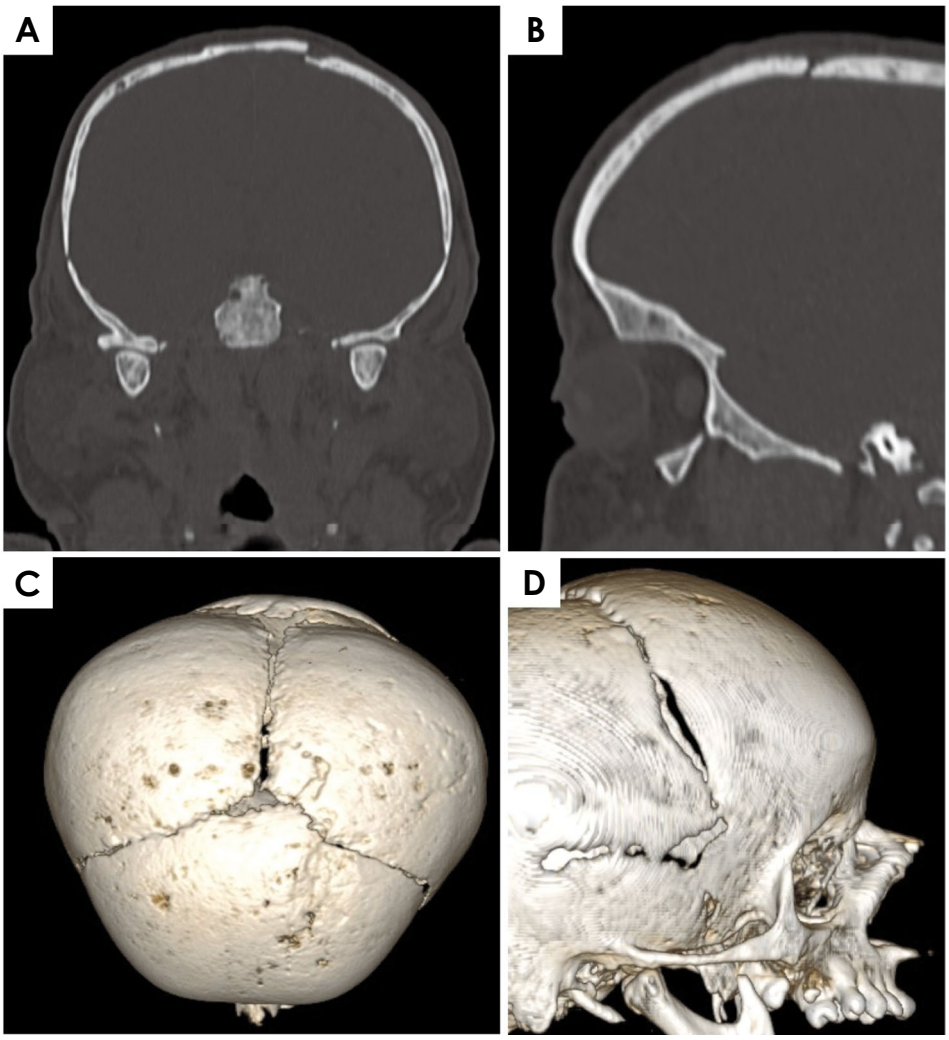

Fig. 4. Discontinuity of the cranial vault is evident on cone-beam computed tomography coronal (A) and sagittal (B) reconstructions. C and D. Three-dimensional reconstruction images show open sutures and fontanelles, as well as frontal and parietal bosses.

quate to suggest a diagnosis of PYCD, even in the absence of clinical symptoms.

Therefore, it is important to highlight that the findings of the present systematic review identified the primary craniofacial imaging features of PYCD. These features include delayed cranial suture closure, open fontanelles, cranial bosses, and high bone density. While delayed suture closure is a prominent feature of PYCD, craniosynostosis has also been documented as a characteristic of the condition in prior research.[4,13,19,59,64] Nonetheless, craniosynostosis was observed infrequently in the studies covered by this systematic review, occurring in only 13.4% of cases.

Obtuse mandibular angle, a key diagnostic feature that distinguishes PYCD from cleidocranial dysplasia, was observed in 84.3% of the present sample. This observation supports the findings of Sayed Amr et al.,[13] Doherty et al.,[7] Markova et al.,[49] Sait et al.,[4] and Verma and Singh.[87]

Few studies have been published that describe the oral clinical and radiographic changes associated with PYCD.[5,13,57,59] In this systematic review, the most frequently observed oral abnormalities were micrognathia (found in 62.6% of cases), malocclusion (59.2%), and dental crowding (54.2%).

Previous research[5,13,59] has indicated that patients with PYCD can exhibit multiple dental anomalies, including enamel hypoplasia, obliterated pulp chambers, delayed eruption, tooth agenesis, hypercementosis, and ectopic teeth. In the present review, tooth agenesis was the most frequently observed anomaly, present in 15.6% of the 179 cases evaluated. Notably, most articles assessed in this review did not provide information on clinical and dental examinations of patients, which may have resulted in underreporting of these anomalies.

Patients diagnosed with PYCD experience an impaired capacity to effectively remodel bone, leading to a generalized increase in bone density and sclerosis. This condition

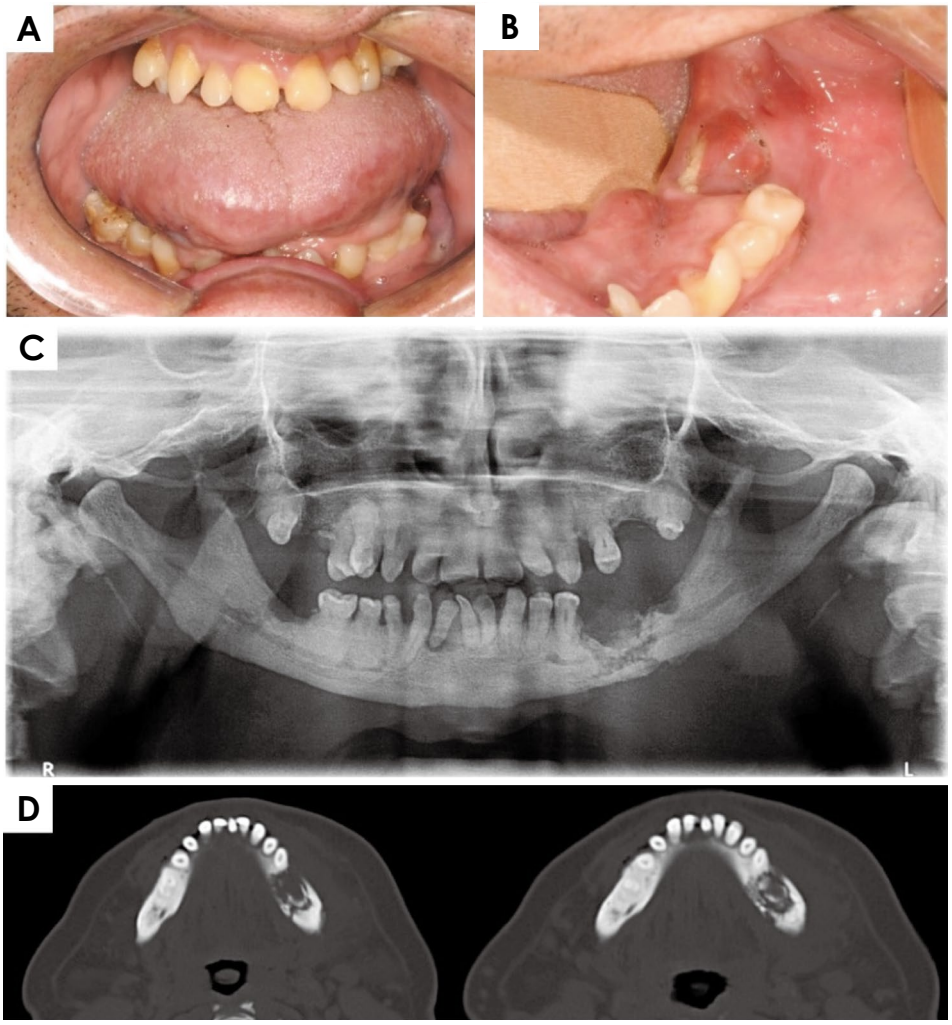

Fig. 5. A. Intraoral photograph shows malocclusion and enamel hypoplasia. B. Intraoral photograph reveals intraoral fistula, which is compatible with the clinical diagnosis of osteomyelitis. C. Panoramic radiograph illustrates increased bone density, obtuse mandibular angle, missing teeth, and the presence of an osteolytic lesion in the body of the left mandible, accompanied by areas of bony sequestrum. D. Axial cone-beam computed tomographic images of the mandible depicts a hypodense line in the lingual mandibular cortex, compatible with a pathological fracture.

increases their susceptibility to bone fractures; however, these fractures tend to occur in the long bones.[4] In the present systematic review, only 7 of the 179 patients exhibited fractures of the craniofacial bones.

Among the oral manifestations noted in patients with PYCD, osteomyelitis is the most serious. In the gnathic bones, local factors associated with the development of osteomyelitis include continuous trauma, alveolar surgical intervention, and infection.[5,6] Severity aside, the present systematic review revealed a relatively low frequency of osteomyelitis in the maxillary bones, affecting 7.3% of the examined cases.

According to a systematic review carried out by França et al.,[6] tooth extraction was identified as the primary risk factor associated with the development of osteomyelitis in patients with PYCD. This was followed by a history of mandibular fracture and the presence of infections, including caries and periodontal disease. In terms of anatomical location, the mandible was the most frequently impacted bone. The most common symptoms observed were edema, pain, purulent discharge, fistula formation, and trismus. Treatment for osteomyelitis can vary from conservative methods, such as antibiotic therapy and curettage, to more aggressive strategies, including tooth extraction and surgical resection.

The current approach to managing PYCD is multidisciplinary and focuses primarily on managing symptoms, with an emphasis on fracture prevention. To prevent osteomyelitis, clinicians should convey the importance of daily oral hygiene, while providing antibiotic prophylaxis in cases of tooth extraction.[16] Dental professionals should be aware of the primary characteristics of PYCD, as this knowledge is key to early diagnosis of the syndrome. Early detection enables more effective management and helps prevent subsequent complications, improving patient quality of life.

The heterogeneity of the studies included in this systematic review precluded the use of meta-analysis for statistical evaluation of the data gathered. Nevertheless, despite this

Table 5. Summary of CARE checklist item scores

No.	Item	Frequency (out of 84, %)
01	Diagnosis or intervention of primary focus, followed by the words "case report"	51 (60.7%)
02	Two to 5 key words that identify diagnoses or interventions in this case report, including "case report"	46 (54.7%)
03a	Introduction: What is unique about this case and what does it add to the scientific literature?	53 (63.0%)
03b	Main symptoms and/or important clinical findings	45 (53.5%)
03c	Main diagnoses, therapeutic interventions, and outcomes	55 (65.4%)
03d	Conclusion—What is/are the main "take-away" lesson(s) from this case?	39 (46.4%)
04	One or 2 paragraphs summarizing why this case is unique (may include references)	77 (91.6%)
05a	De-identified patient-specific information	83 (98.8%)
05b	Primary concerns and symptoms of the patient	76 (90.4%)
05c	Medical, family, and psychosocial history, including relevant genetic information	83 (98.8%)
05d	Relevant past interventions with outcomes	68 (80.9%)
06	Descriptions of key physical examination (PE) and clinical findings	84 (100%)
07	Historical and current information from this episode of care organized as a timeline	58 (69.0%)
08a	Diagnostic testing (such as PE, laboratory testing, imaging, surveys)	82 (97.6%)
08b	Diagnostic challenges (such as access to testing, financial obstacles, or cultural challenges)	33 (39.2%)
08c	Diagnosis (including other diagnoses considered)	83 (98.8%)
08d	Prognosis (such as staging in oncology) where applicable	Not applicable
09a	Types of therapeutic intervention (such as pharmacologic, surgical, preventive, self-care)	Not applicable
09b	Administration of therapeutic intervention (such as dosage, strength, duration)	Not applicable
09c	Changes in therapeutic intervention (with rationale)	Not applicable
10a	Clinician and patient-assessed outcomes (if available)	Not applicable
10b	Important follow-up diagnostic and other test results	53 (63.0%)
10c	Intervention adherence and tolerability (How was this assessed?)	Not applicable
10d	Adverse and unanticipated events	Not applicable
11a	A scientific discussion of the strengths AND limitations associated with this case report	81 (96.4%)
11b	Discussion of the relevant medical literature with references	82 (97.6%)
11c	Scientific rationale for any conclusions (including assessment of possible causes)	82 (97.6%)
11d	Primary "take-away" lessons of this case report (without references) in a 1-paragraph conclusion	58 (69.0%)
12	Sharing by the patient of their perspective, in 1 to 2 paragraphs, regarding the treatment(s) received	1 (1.1%)
13	Did the patient give informed consent? Please provide if requested	27 (32.1%)

limitation, the study provides a comprehensive examination of the clinical and imaging features of PYCD, establishing the principal characteristics for its early diagnosis.

The findings of this systematic review confirm that PYCD is a rare condition that predominantly affects children of consanguineous parents. Female patients were slightly more common than male patients, and the mean age fell within the second decade of life. PYCD is characterized by short stature, acroosteolysis, brachydactyly, prominent nose, exophthalmos, and hypoplasia of the middle third of the face. Notable oral and craniofacial abnormalities include an obtuse mandibular angle, frontal bosses, open fontanelles and cranial sutures, and increased bone density in the craniofacial region. Patients may also exhibit micrognathia, malocclusion, dental crowding, and a narrow, grooved palate.

Conflicts of Interest: None

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