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Review Article

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Mariné Olmos Villagomez, Taíssa Cássia de Souza Furtado, Maya Fernanda Manfrin Arnez, Fabrício Kitazono de Carvalho, Alexandra Mussolino de Queiroz, Francisco Wanderley Garcia de Paula-Silva.

Mariné Olmos Villagomez, DDS,
MSc Student, Department of Pediatric Dentistry, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil
Avenida do Café, s/n., Ribeirão Preto – São Paulo, Brazil – 14040-904
E-mail: marine.olmos@usp.br

Taíssa Cássia Furtado, DDS, MSc,
PhD Student, Department of Pediatric Dentistry, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil
Avenida do Café, s/n., Ribeirão Preto – São Paulo, Brazil – 14040-904
E-mail: taissacassia@usp.br

Maya Fernanda Manfrin Arnez, DDS, MSc, PhD
Associate Professor, Department of Pediatric Dentistry, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil
Avenida do Café, s/n., Ribeirão Preto – São Paulo, Brazil – 14040-904
E-mail: mayaarnez@alumni.usp.br

Fabrício Kitazono de Carvalho, DDS, MSc, PhD
Associate Professor, Department of Pediatric Dentistry, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil
Avenida do Café, s/n., Ribeirão Preto – São Paulo, Brazil – 14040-904
E-mail: fabricio_kc@forp.usp.br

Alexandra Mussolino de Queiroz, DDS, MSc, PhD
Associate Professor, Department of Pediatric Dentistry, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil
Avenida do Café, s/n., Ribeirão Preto – São Paulo, Brazil – 14040-904
E-mail: amqueiroz@forp.usp.br

Francisco Wanderley Garcia de Paula-Silva, DDS, MSc, PhD
Associate Professor, Department of Pediatric Dentistry, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil
Avenida do Café, s/n., Ribeirão Preto – São Paulo, Brazil – 14040-904
E-mail: franciscogarcia@forp.usp.br
ORCIDs:
MOV: 0009-0008-5009-7740
TCSF: 0000-0002-8186-1798
MFMA: 0000-0002-1044-0937
FKC: 0000-0002-4837-0583
AMQ: 0000-0003-2900-5000
FWGPS: 0000-0001-8559532X

AUTHORS' CONTRIBUTIONS

MOV: Data adquisition, revising the article for important intellectual content, final approval of the version to be submitted.
TCF: Resources provisioning, supervision, conception and design of the tables, revising the article for important intellectual content, final approval of the version to be submitted.
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FKC: Analysis and interpretation of the tables, revising the article for important intellectual content, final approval of the version to be submitted.
AMQ: Revising the article for important intellectual content, final approval of the version to be submitted.
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This review underscores the critical role of recognizing rare diseases and their oral manifestations in medical and dental practice, especially pediatric dentistry, understanding these rare diseases is crucial. Many present specific oral symptoms, making dental professionals pivotal in early recognition and intervention. With genetic origins predominating, especially in cases diagnosed during childhood, pediatric dentists are uniquely positioned to identify atypical oral presentations that may indicate a rare condition. This early detection can lead to timely referrals and contribute to multidisciplinary management, helping prevent disease progression and improve patient outcomes. The publication of this work will expand healthcare professionals' understanding of the relationship between rare diseases and oral manifestations, facilitating the implementation of evidence-based clinical approaches and promoting interdisciplinary collaboration in comprehensive patient management.

Rare Diseases and Oral Manifestations: What Pediatric Dentists Should Know?

Short Title: Rare Diseases and Oral Manifestations?

Abstract

A rare disease affects up to 65 people per 100,000 or 1.3 per 2,000 individuals. These diseases present a variety of signs and symptoms that can vary between individuals and often resemble more common conditions, complicating early diagnosis. Rare diseases are typically chronic, progressive, and fatal, severely impacting the quality of life. They may lead to the loss of autonomy in basic functions such as walking, eating, or breathing, resulting in clinical and psychosocial suffering for both patients and their families. Most rare diseases are incurable, with treatment focused on managing symptoms, preventing progression, and reducing complications. Treatment is often handled by multidisciplinary teams. Oral care depends on the patient's overall condition and should follow standardized protocols where available, tailored to the patient's specific needs. Genetic alterations are the cause of most rare diseases, with 75% diagnosed in childhood. Many of these diseases present oral manifestations, making it crucial for pediatric dentists to recognize their significance for early diagnosis, patient referral, and treatment. Given the prevalence of rare diseases and their oral implications, it is essential for healthcare professionals to be knowledgeable about their management and

appropriate clinical approaches. This paper aims to review basic concepts about rare diseases and their oral manifestations.

Keywords: rare diseases; dental care; pediatric dentists; children; oral manifestations

INTRODUCTION

A rare disease is considered to be one that affects up to 65 people per 100,000 individuals or 1.3 people per 2,000 individuals according to the WHO.[1] The exact number of rare diseases that exist is not known, but it is estimated that there are between 6,000 and 8,000 different types worldwide. According to the Ministry of Health, 13 million Brazilians live with a rare disease, the vast majority of them without having a specific treatment, leaving only palliative care and rehabilitation.Rare diseases have multiple signs and symptoms and change from disease to disease and from person to person affected by the same condition. Although they are considered rare conditions, together they affect a significant percentage of the population, resulting in a significant public health problem.[2] Some of these diseases are genetic in origin and are potentially fatal.[3] The definition and identification criteria for rare diseases may vary by country or region. In many parts of the world, the term rare disease is used as a synonym for "orphan disease" due to a lack of information, diagnostic support, and related therapeutic interventions.[3] About 75% of rare diseases are diagnosed in childhood, with about 30% of patients dying before they turn five years old. In addition, it often presents manifestations in the oral cavity in

various ways. This makes it essential for pediatric dentists to understand its relevance for early diagnosis, proper patient referral, and precise therapeutic intervention. This article aims to summarize the basic concepts, oral manifestations, and clinical considerations of these rare disease-related pathologies, providing understanding and diagnostic tools that pediatric dentists can apply in their daily practice to improve patients' quality of life.

LITERATURE REVIEW

According to the Ministry of Health, 13 million Brazilians live with a rare disease, the vast majority of them without having a specific treatment, leaving only palliative care and rehabilitation.[2] In Brazil, there are 62 PDCTS (Programs for the Diagnosis and Treatment of Rare Diseases), The vast majority of rare diseases affect children and among the professionals specialized in the area, the pediatric dentist plays a fundamental role in the detection of oral signs associated with rare diseases, such as changes in tooth structure, late tooth eruption, craniofacial anomalies and pathologies of the oral mucosa. Its ability to recognize these manifestations facilitates early diagnosis, contributing to multidisciplinary management and improving therapeutic interventions. Rare diseases have been reclassified as new genetic advances emerge, allowing the subdivision of conditions that were previously grouped into a single category.[6] Currently, these diseases are classified according to their nature into two large groups: those of genetic origin, which correspond to about 80% of cases, and those of non-genetic origin. Among genetic diseases, congenital anomalies, intellectual disabilities, and inborn errors of metabolism stand out. On the other hand, diseases of non-genetic origin, which represent a smaller proportion, include infectious, inflammatory, autoimmune conditions, among others.[2-5] Congenital anomalies comprise functional or structural anomalies in the development of the fetus, resulting from some factor that originated before birth, whether genetic, environmental, or unknown, even if the defects are not

noticeable in the newborn and manifest later.[7-8] The clinical manifestations of rare diseases can often resemble common diseases, making their diagnosis difficult.[6] Many of these diseases are known for their unique and complex characteristics, which can lead to chronic clinical impairments and gradually interfere with the social, physical, and psychological aspects of individuals' daily lives.[5] Generally, these diseases are chronic, progressive, degenerative and life-threatening, affecting the quality of life of those affected.[2] Clinical manifestations of rare diseases can be complex and similar to those of more common diseases, which makes their early diagnosis difficult. These conditions are chronic, progressive and degenerative, which significantly affects the quality of life of the patient and their surroundings. In oral terms, diseases such as ectodermal dysplasia, osteogenesis imperfecta and mucopolysaccharidosis present notable changes such as hypodoncia, malocclusion, macroglossia and defects in tooth enamel (Table 1).

TABLE 1.- Rare diseases:

Disease	**Diagnostic Criteria**	**Craniofacial and Oral Manifestations**	**Dental Treatment**
Ectodermal Dysplasia	Family history and genetic testing.	Hypodontia, anodontia, cone-shaped teeth, enamel defects, xerostomia, increased oral bacterial load.	Topical fluoridation, sealants, prosthetics, dental implants, composite restorations for younger children.
Williams-Beuren Syndrome	Identification of typical facial features, genetic testing (FISH), echocardiography.	Micrognathia, prominent lips, small or irregular teeth, bruxism, xerostomia, delayed tooth eruption.	Preventive care, occlusal splints for bruxism, prosthetic solutions for missing teeth, regular dental monitoring.

Congenital Erythropoietic Porphyria	Family history, photosensitivity symptoms, autosomal recessive inheritance.	Reddish teeth with fluorescence under UV light, well-defined discoloration, and bone resorption.	Fluoride varnish to protect enamel, cosmetic dental management, and preventive oral care.
Osteogenesis Imperfecta	Genetic mutations in the COL1A1 or COL1A2 genes, autosomal dominant inheritance.	Macrocephaly, midface hypoplasia, dentinogenesis imperfecta, malocclusions, delayed tooth eruption.	Aesthetic restorations, orthodontic treatment, prosthetics, radiographic assessments for structural issues.
Hypophosphatemic Rickets	Persistent hypophosphatemia, confirmed by genetic testing.	Enamel hypoplasia, taurodontism, recurrent abscesses or fistulas, delayed tooth eruption.	Infection control, restorative care, fluoride application, and prosthetic rehabilitation as needed.
Hypophosphatasia	Low alkaline phosphatase levels, ALPL gene mutations.	Premature loss of primary teeth, enamel hypoplasia, enlarged pulp chambers, defective cementum formation.	Restorative treatment for fragile teeth, prosthetic or orthodontic management, and preventive fluoride treatments.
Marfan Syndrome	Systemic manifestations meeting Ghent criteria, FBN1 gene mutations, family history.	High-arched palate, retrognathia, midface hypoplasia, and potential malocclusion.	Orthodontics for malocclusion, aesthetic and functional restorations, preventive dental care for periodontal issues.

McCune-Albright Syndrome	Clinical triad: café-au-lait spots, fibrous dysplasia, and endocrine hyperfunction.	Facial asymmetry from fibrous dysplasia, dental malocclusion, taurodontism, high risk of caries, and delayed tooth eruption.	Conservative restorations, orthodontics for malocclusion, surgical correction for severe bone deformities, and preventive care.
Fanconi Anemia	Chromosomal breakage tests and genetic confirmation.	Increased risk of oral squamous cell carcinoma, enamel hypoplasia, malformed teeth, and delayed tooth eruption.	Regular cancer screenings, restorative care for enamel defects, and careful handling during dental procedures due to pancytopenia.
Kallmann Syndrome	Genetic testing for FGFR1, KAL1 mutations; anosmia and delayed puberty.	Cleft palate, high-arched palate, micrognathia, malformed teeth, and hypodontia.	Orthodontic corrections, prosthetic replacements, and surgical or prosthetic management of cleft palate complications.
Peutz-Jeghers Syndrome	Hyperpigmented macules on lips, oral mucosa, and extremities; confirmed by genetic testing (STK11 mutations).	Flat, dark brown or black macules on the lips, gingiva, and buccal mucosa. These do not affect dental health but may raise aesthetic concerns.	Aesthetic management (e.g., laser treatment) if desired by the patient. Regular monitoring of the oral mucosa for potential changes or associated lesions.

Mucopolysaccharidosis (MPS)	Elevated urinary glycosaminoglycan levels, enzymatic activity tests, and genetic testing for specific subtypes.	Coarse facial features, macroglossia, high-arched palate, malocclusion, delayed tooth eruption, increased risk of caries.	Preventive care with fluoride, orthodontics for malocclusions, restorative treatments for caries, and prosthetic solutions for lost teeth.
Primary Light-Chain Amyloidosis (AL)	Tissue biopsy with Congo red staining confirming amyloid deposits; serum and urine protein electrophoresis.	Macroglossia causing difficulty in speech and mastication; submucosal plaques or nodules in the oral cavity.	Management of macroglossia (e.g., prosthetic adjustments), preventive dental care to reduce caries risk, and functional restorations for affected teeth.
Mikulicz Disease (IgG4-Related Disease)	Biopsy of salivary glands showing IgG4-positive plasma cells; elevated serum IgG4 levels.	Painless enlargement of the salivary and lacrimal glands, xerostomia leading to difficulties in speech and eating.	Saliva substitutes and stimulants, meticulous oral hygiene to prevent caries, and regular dental check-ups to monitor oral health.
Epidermolysis Bullosa (EB)	Genetic testing to identify mutations in genes affecting skin and mucosa; skin biopsy with immunofluorescence.	Intraoral blistering, enamel hypoplasia, severe ankyloglossia, and a high prevalence of caries due to oral hygiene challenges.	Gentle oral care practices, topical fluoride for enamel protection, conservative restorations, and trauma-free dental procedures.
Edwards Syndrome (Trisomy 18)	Karyotype analysis confirming trisomy 18. Characteristic physical features, including	Micrognathia, cleft palate, high and narrow palate, cone-shaped teeth,	Multidisciplinary care with orthodontics, restorative solutions for malformed teeth,

	micrognathia and malformations of multiple systems.	and delayed tooth eruption.	and prosthetics for severe tooth loss.
Langerhans Cell Histiocytosis (LCH)	Biopsy of bone lesions and immunohistochemistry confirming CD1a+ and S100+ Langerhans cells.	Jawbone lesions causing mobility of teeth, gingival necrosis, and alveolar bone destruction.	Surgical management of lesions, conservative restorations, and extractions for severely affected teeth.
Goldenhar Syndrome (Oculo-Auriculo-Vertebral Dysplasia)	Clinical diagnosis based on unilateral craniofacial asymmetry, ocular, auricular, and vertebral anomalies.	Unilateral hypoplasia of the maxilla or mandible, cleft palate, hypodontia, and malocclusion.	Orthodontic treatment for malocclusion, surgical corrections for cleft palate or facial asymmetry, and prosthetic solutions for missing teeth.
Solitary Maxillary Central Incisor Syndrome	Single central incisor confirmed through clinical evaluation and imaging; genetic testing for associated anomalies.	A single maxillary central incisor, narrow palate, and absence of the upper labial frenum.	Orthodontic management for alignment, prosthetic or restorative solutions for aesthetic improvement.

DENTAL TERMINOLOGY IN THE CONTEXT OF PEDIATRIC DENTISTRY AND RARE DISEASES.

- **Anodontia**: The total absence of tooth germs, which can affect both primary and permanent teeth.
- **Bruxism**: A habit of grinding or clenching the teeth, which can lead to dental wear and jaw pain.
- **Dental Erosion**: The wear of tooth enamel caused by exposure to acids, without bacterial intervention.

- **Diastema**: A space or gap between two teeth, typically observed between the upper incisors.
- **Dentinogenesis Imperfecta**: An inherited disorder affecting dentin formation, leading to fragile, discolored teeth that are prone to fractures.
- **Enamel Hypoplasia**: A developmental defect in tooth enamel, making it thin, fragile, and more susceptible to cavities.
- **Gingivitis**: Inflammation of the gums caused by plaque bacteria, with symptoms including redness, swelling, and bleeding.
- **Hypodontia**: A congenital condition characterized by the congenital absence of one or more teeth, excluding third molars. It can affect both primary and permanent teeth.
- **Macrocephaly**: An excessively large head size, generally associated with cranial or neurological anomalies.
- **Macroglossia**: An abnormally large tongue, which can cause issues with speech, swallowing, or breathing.
- **Microbrachycephaly**: A small, flattened skull in the posterior region, related to developmental anomalies.
- **Micrognathia**: A condition in which the lower jaw is underdeveloped, leading to potential issues with bite, breathing, and speech.
- **Midfacial Hypoplasia**: Underdevelopment of the middle third of the face, which can affect both aesthetics and function.
- **Oligodontia**: A rare condition where six or more teeth are missing, either primary or permanent, due to developmental failure.
- **Osteosarcoma**: A malignant tumor originating in bone tissue, commonly in long bones but can also affect the jawbones.
- **Plagiocephaly**: A cranial deformity characterized by an asymmetric flattening of part of the skull.
- **Prognathism Mandibular**: Excessive projection of the lower jaw, which affects both dental alignment and facial aesthetics.
- **Retained or Impacted Teeth**: Teeth that have failed to erupt at the expected time and remain within the jawbone.
- **Strabismus**: An abnormal alignment of the eyes, resulting in misaligned vision or double vision.
- **Taurodontism**: A dental anomaly where the pulp chamber is larger than normal, with short roots and an enlarged body of the tooth.
- **Xerostomia**: A condition characterized by dry mouth due to a reduction or absence of saliva production.

The recognition of these manifestations is crucial for the differential diagnosis and the derivation of multidisciplinary equipment. Pediatric dentists should be able to identify craniofacial features such as micrognathia, mandibular prognathism and

arcuate palates, which can coexist with dental and systemic changes.[3-9-12](Table 1)

Table 2. Rare diseases with oral manifestations.

Rare disease	**Oral manifestation**
Ectodermal dysplasia	• Congenital hypodontia, oligodontia or anodontia (deciduous and permanent dentition); • Changes in tooth morphology or size – conoid-shaped teeth, taurodontism, and enamel developmental defects, including hypoplasia; • Decreased salivary secretion, reduced buffering capacity and increase bacterial load in oral cavity.
Williams-Beuren syndrome	• Malar flattening; • Small lower jaw (micrognatia); • Wide mouth with voluminous lips; • Small or unusually shaped primary teeth; • Malocclusions with diastema; • Hypodontia and enamel development defects.

Congenital erythropoietic porphyria (Gunther's disease)	• Extensive bone resorptions; • Tooth exhibits fluorescence when using long-wavelength ultraviolet light due to porphyrin deposition during tooth development; • Visible reddish-brown tooth discoloration with well-defined margin.
Osteogenesis imperfecta	• Dentinogenesis imperfecta.
Hypophosphatemic rickets	• Recurrent abscesses or sinus tracts associated with dental caries; • Microdefects in enamel, especially in anterior teeth; • Enamel hypoplasia and lack of fusion of chalcospherites in dentin, facilitating microbial penetration – pulp infection, pulp necrosis, periapical periodontitis, abscesses; • Delayed tooth eruption; • Taurodontism – large pulp chambers, short roots, prominent pulp horns, thin layer of enamel; • Hypoplastic alveolar crest.

Hypophosphatasia	• Premature loss of primary teeth, especially anterior teeth; • Large pulp chambers; • Impaired dentinogenesis; • Enamel hypoplasia; • Joint pain; • Recurrent fractures; • Cupped form teeth; • Cemental hypoplasia; • Early loss of permanent teeth.
Marfan syndrome	• Arched high palate; • Midface hypoplasia; • Mandibular retrognathia; • Malar hypoplasia.

McCune-Albright syndrome	• Facial asymmetry due to an expanding polyostotic fibrous dysplasia lesion, which may progress to dental malocclusion; • Dentin dysplasia; • Taurodontism; • High dental caries risk; • Polyostotic fibrous dysplasia of the mandible may contribute to aneurysmal bone cysts and osteosarcoma.
Kallmann syndrome	• Cleft palate and lip; • High arched palate; • Hypodontia; • Malformed teeth; • Increased tendency of bone fractures
Fanconi anemia	• Risk of solid tumors or cancers (mainly squamous cell carcinomas of the head and neck).

Epidermolysis bullosa	• *Light form* – oral mucosa with discrete blisters that heal quickly without leaving scars. *Severe form* – The entire oral mucosa may be affected and severe intraoral blisters may be seen with subsequent scarring; • Extensive introral scarring can cause ankyloglossia and obliteration of the oral vestibule; • Enamel hypoplasia, mainly in junctional epidermolysis bullosa; • Dental caries, mainly in junctional bullae epidermolysis, due to enamel hypoplasia, decreasing the intrinsic resistance of the tooth. In dystrophic epidermolysis bullosa, caries is associated with diet and limited mobility of the tongue.
Peutz-Jeghers syndrome	• Hyperpigmented macules ranging from 1 to 5 mm in size on the lips and oral mucosa (often on the gums, hard palate, and inside the cheek) – flat and painless.

Mucopolysaccharidosis	• Increased volume of the tongue; • Dental caries; • Gingivitis; • Enamel development defects; • Malocclusion; • Enlarged mouth and hypertrophied lips; • Increase in the volume of the gingiva; • Anterior open bite; • High arched palate; • Hypertrophy of alveolar processes; • Delayed tooth eruption.
Mikulicz's disease	• Dry mouth; • Continuous, painless, bilateral and symmetrical enlargement of the salivary glands – usually involves the parotid, submandibular, occasionally sublingual salivary glands; • Non-ulcerated, painless, irregular swelling of the left hard palate; • If combined with another IgG4-RD disease, it can cause extra salivary gland damage.

Primary light chain amyloidosis	• Macroglossia; • Submandibular edema.
Angelman syndrome	• Speech impairment; • Impaired oral motor functions, such as sucking and chewing; • Protruding tongue; • Mandubular prognathism; • Wide mouth; • Generalized diastemas.
Langerhans cell histiocytosis	• Ulcers, crusts and granuloma with pain and swelling of the oral mucosa region; • Bone lesions in the mandible, initially which may present as cysto or granuloma around the teeth; • Gingival necrosis with tooth movement and alveolar bone destruction – most common.

Edwards syndrome (trisomy 18)	• Micrognathia; • Cleft lip; • High, narrow and sometimes cleft arched palate; • Small mouth with limited oral opening; • Gingival inflammation; • Multiple carious lesions; • Deviated midline; • Bilateral posterior crossbite; • Anterior crossbite; • Anterior open bite with tongue positioned on the incisive papilla during rest; • Tooth agenesis; • Taurodontism and shortened roots; • Ectopic eruption; • Partial impactions and tooth displacement; • Tooth changes in size, conical shape.
Goldenhar syndrome	• Unilateral maxillary and malar hypoplasia; • Palatal clefts; • Hypodontia in permanent dentition; • Impacted teeth; • Angle Class II molar relationship.

Solitary maxillary central incisor syndrome	• Single maxillary central incisor that can affect the deciduous and permanent dentition; • Arched upper lip; • Undefined or short filter; • Narrow palate; • Absent or abnormal intermaxillary sutures in the region of the incisive foramen. • Superior labial frenulum absent; • Absence of incisive papilla.

The management of rare diseases generally implies multidisciplinary teams that address the specific needs of the patient. In dentistry, strategies include restorative, preventive, and adaptive treatments. For example, in patients with severe hypodoncia, it is essential to plan oral rehabilitation with removable prostheses or dental implants, depending on the patient's age and systemic condition. In addition, the care protocols should consider the fragility of oral patients and the physical limitations associated with the disease.[6] The role of the pediatric dentist is not limited to clinical management; it also includes guidance to families and collaboration with other specialists to optimize the general care of the patient. Numerous efforts by the rare disease support community and the Brazilian Ministry of Health have resulted in an increase in probable diagnoses and interventions, although several rare diseases remain under-covered.[13] In recent decades, social interest in rare disease patients has increased and a current social progress has been the increase in the quality of care provided to these individuals. Providing improvement in quality of life and social well-being is very important for affected individuals, as well as for the

community.[6] However, care for rare diseases in the Unified Health System (SUS) in Brazil is carried out in Primary Care and, if necessary, the individual is referred to specialized care in a medium or high complexity unit. Care is provided by multidisciplinary teams in several health units throughout the country, such as primary care units, specialized rehabilitation centers, teaching university hospitals, and other hospital units.[2] In Brazil, the public health system is the main source of diagnosis and treatment of rare diseases.[5] The National Policy for Comprehensive Care for People with Rare Diseases has been adopted since 2014, aiming at the prevention, diagnosis, treatment, and rehabilitation of individuals with rare diseases, with the aim of facilitating access to information and health services, reducing disability caused by these diseases, and supporting the improvement of people's quality of life.[2] The procedures for diagnosing rare diseases follow the guidelines of the ordinance that enables the services and the performance of procedures in the Outpatient Information System (SIA/SUS) and are financed by the Strategic Actions and Compensation Fund (FAEC) at the Municipal, State or Federal level. Currently, the Ministry of Health has 17 qualified and specialized establishments distributed in several federative units of Brazil that aim to provide care to Rare Diseases.[2] Currently, the Clinical Protocols and Therapeutic Guidelines approved by the National Commission for the Incorporation of Technologies in the SUS for 36 rare diseases have already been instituted, which guide all health professionals on how to carry out the diagnosis, treatment and rehabilitation of patients, as well as guide the obtaining of pharmaceutical assistance in the SUS.[2] Dental professionals can collaborate with screening and treatment programs for rare diseases, based on the training of dentists to provide dental care to these groups of patients, who are often neglected in terms of access to services and at increased risk of developing various oral diseases.[6] Specialized outpatient and hospital care covers emergency actions and services, rehabilitation services, specialized outpatient and hospital scope, covering primary care services effectively and in a timely manner. Specialized Care Services and Reference Services for Rare Diseases are responsible for preventive, diagnostic and therapeutic actions for people with rare diseases or who are at risk

of developing them. The Specialized Rehabilitation Centers (CER) are part of the proposal, which are responsible for the rehabilitation of people with disabilities, thus carrying out the treatment, concession, adaptation and maintenance of assistive technology, being a model for the health care network in the territory. In addition, multiprofessional home care is feasible, which acts according to the needs of patients and promotes access to care, diagnosis, and treatment by specialists in rare diseases.[2] The newborn's heel prick test is a method traditionally used to screen for diseases, preferably performed between the 3rd and 5th day of the baby's life, and is mandatory for children born in Brazil. The exam is performed by collecting drops of blood from the newborn's foot, with the aim of identifying disorders and diseases in a timely manner to start appropriate treatment, enabling a reduction in morbidity and mortality and improving the quality of life of patients. children with positive tests.[2] The classic test, offered free of charge by SUS, allows the detection of six diseases: phenylketonuria, congenital hypothyroidism, sickle cell syndrome, cystic fibrosis, congenital adrenal hyperplasia and biotinidase deficiency. The expanded test, to screen for up to 100 diseases, can be performed in private services, by choice of the family. As of 2021, after the enactment of Law No. 14,154, the Newborn Heel Prick Rapid Test offered by SUS will be expanded to include 50 screened diseases, covering 14 groups of diseases. The expansion of the test will detect diseases related to excess phenylalanine, pathologies related to hemoglobin, congenital toxoplasmosis, high level of galactose in the blood, aminoacidopathies, urea cycle disorder, fatty acid beta-oxidation disorders, diseases that affect cell functioning, genetic problems in the immune system and spinal muscular atrophy.[2] Most rare diseases are genetically determined, so genetic counseling in the care of families and people with these diseases is essential. Genetic counseling is a form of communication carried out by a trained multidisciplinary team, containing a geneticist and/or trained health professionals, who deal with problems associated with the occurrence or risk of occurrence of a genetic disease in a family, in addition to non-governmental support groups representing people who meet voluntarily and who share common interests and goals.[14]

DISCUSSION

Rare diseases can encompass a wide variety of conditions that affect dentocraniofacial structures, including dental anomalies, of flat and bone tissues. These manifestations can be key in early diagnosis and in the planning of clinical treatment. For example, characteristics such as imperfect dentinogenesis in imperfecta osteogenesis or macroglossia in mucopolysaccharidosis illustrate how oral and craniofacial signs can guide the differential diagnosis and allow more timely interventions. [15] One of the main straight in the management of rare diseases is the differentiation between their oral manifestations and more common conditions. Enamel hypoplasia, dental malformation, and maxillary alterations can be observed in multiple genetic disorders, making it difficult to identify a specific condition. Recent studies suggest that a multidisciplinary approach, which involves pediatric dentists, geneticists and other specialists, is essential to ensure an accurate diagnosis and an effective treatment.[15-16] Dental management of patients with rare diseases should be carefully adapted. For example, in cases of fibrous dysplasia, it is recommended to avoid invasive procedures due to the risk of accelerated bone regeneration. On the other hand, dental restorations are essential for patients affected by dentinogenesis imperfecta, since intracoronal restorations are not adequately retained in these compromised structures. In addition, the implementation of preventive treatments, such as the application of fluoride and the use of adapted prostheses, can significantly improve the quality of life of patients.[17] Although knowledge about rare diseases has grown, there are no significant limitations, such as the lack of specific clinical guidelines and robust longitudinal studies. Future research should focus on developing dental protocols that address the particularities of these conditions and evaluating the impact of different interventions on the quality of life of patients. Likewise, it would be valuable to establish clinical databases that integrate information on oral and craniofacial manifestations, facilitating access to relevant data for health professionals.

CONCLUSION

Rare diseases, even though individually and frequently, have a significant collective impact on public health and on the quality of life of patients. This narrative review has highlighted the most relevant oral manifestations and their characteristics for early diagnosis, appropriate management and reference to multidisciplinary teams. Pediatric dentists play a crucial role in the clinical management of these alterations, but also in the orientation of families and collaboration with other health professionals. The dental care of these patients requires a personalized approach that considers the particularities of each disease, using specific protocols and adaptive strategies to minimize complications and improve quality of life. However, the current literature has significant limitations, such as the lack of extensive studies and specific clinical guidelines for the management of rare diseases in pediatric dentistry. In conclusion, the knowledge of oral manifestations of rare diseases is essential for pediatric dentists. This study reflects the importance of continuous training and interdisciplinary work to optimize the care of these patients and contribute to their general well-being.

References

1. Denis A, Simoens S, Fostier C, Mergaert L, Cleemput I. Policies for rare diseases and orphan drugs. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2009. KCE 112C reports (D/2009/10.273/32).
2. Brazil. Minister is Rio da Saú de . Secretariat of Health Care. Department of Specialized and Thematic Care. General Coordination of M is day and High Complexity. Guidelines for Comprehensive Care for People with Rare Diseases in the Unified Health System – SUS / Ministry of Health . Secretariat of Health Care. Department of Specialized and Thematic Care. General Coordination of

M is day and High Complexity. Brazil : Minist is a river of Health , 2014. 41 p.

3. Luo E, Liu H, Zhao Q, Shi B, Chen Q. Dentocraniofacial manifestation and treatment of rare diseases. Int J Oral Sci. 2019 Feb 20; 11(1):9.
4. Vieira DKR, Attianezi M, Horovitz DD, Llerena Jr JC. Medical genetics care in the SUS: the experience of a medium-sized municipality. Física: Revista de Saúde Coletiva [online] 2013, v. 1, p. 243-261.
5. Lopes MT, Koch VH, Sarrubbi -Junior V, Gallo PR, Carneiro-Sampaio M. Difficulties in the diagnosis and treatment of rare diseases according to the perceptions of patients, family members and health professionals. Clinics [online]. 2018, v. 73 , e68.
6. Molina-García A, Castellanos-Cosano L, Machuca-Portillo G, Posada-de la Paz M. Impact of rare diseases on oral health. Med Oral Patol Oral Cir Buccal. September 1, 2016; 21(5):e587-94.
7. Pan American Health Organization . Prevention and control of genetic diseases and congenital defects: relation to the river of a consultation group. Washington DC, 1984. 30p. Publication o Cientí is at 460 .
8. Horovitz DDG, Llerena Jr. JC, Mattos RA. Attention to congenital defects in Brazil: current panorama. Cad Saú de Pública . 2005;21:1055-64.
9. Ribeiro RR, dos Santos BM, Stuani AS, de Freitas AC, de Queiroz AM. Dental findings and dental management in trisomy 18: a case report of a 13-year "long-term survivor". Specific care dentist. 2006 November-December; 26(6):247-51.
10. Garcia de Paula e Silva FW, de Carvalho FK, Diaz-Serrano KV, de Freitas AC, Borsatto MC, de Queiroz AM. Solitary median maxillary central incisor associated with Goldenhar syndrome: case report. Specific care dentist. 2007 May-June; 27(3):105-7.
11. de Carvalho FK, Arid J, De Rossi A, Paula-Silva FW, Nelson-Filho P. Solitary Median Central Maxillary Incisor Versus Maxillary Central Incisor Agenesis. J Dent Child (Chic). 2016; 83(1):29- 32.

12. Ruy Carneiro NC, Duda Deps T, Campos França E, Ribeiro Valadares E, Almeida Pordeus I, Borges-Oliveira AC. Oral health of children and adolescents with mucopolysaccharidosis and a sense of maternal coherence. Specific care dentist. September 2017; 37(5):223-229.
13. Groft SC. Rare disease research: expanding opportunities for collaborative translational research. Chest. 2013 Jul; 144(1):16-23.
14. Lima MAFD, Gilbert ACB; Horovitz DDG. Treatment networks and rare disease patient associations. Ciência e Saúde Coletiva [online]. 2018, v. 10 [Accessed June 16, 2021], pp.
15. Papadopoulou, C. I., Sifakakis, I., & Tournis, S. (2024). Metabolic Bone Diseases Affecting Tooth Eruption: A Narrative Review. Children (Basel, Switzerland), 11(6), 748.
16. Foster, B. L., Ramnitz, M. S., Gafni, R. I., Burke, A. B., Boyce, A. M., Lee, J. S., Wright, J. T., Akintoye, S. O., Somerman, M. J., & Collins, M. T. (2014). Rare bone diseases and their dental, oral, and craniofacial manifestations. Journal of dental research, 93(7 Suppl).
17. Salerno, C., D'Avola, V., Oberti, L., Almonte, E., Bazzini, E. M., Tartaglia, G. M., & Cagetti, M. G. (2021). Rare Genetic Syndromes and Oral Anomalies: A Review of the Literature and Case Series with a New Classification Proposal. Children (Basel, Switzerland), 9(1), 12.

Table 1. Rare diseases and their oral manifestations.