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Syndromes Affecting Craniofacial and Dental Structures

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SYNDROMES AFFECTING CRANIOFACIAL AND DENTAL STRUCTURES

Nossa missão é a difusão do conhecimento gerado no âmbito acadêmico por meio da organização e da publicação de livros científicos de fácil acesso, de baixo custo financeiro e de alta qualidade!

Nossa inspiração é acreditar que a ampla divulgação do conhecimento científico pode mudar para melhor o mundo em que vivemos!

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SUMÁRIO

PRESENTATION

The curricular component of Syndromes Affecting Craniofacial and Dental Structures provides students and teachers with scientific foundations associated with anthropological, technical, and artistic aspects.

There are numerous methodologies to approach the teaching of Syndromes Affecting Craniofacial and Dental Structures. In this book, the content was distributed across ten chapters, ending with a step-by-step overview of the main syndromes Affecting Craniofacial and Dental Structures. The sequence of chapters and their contents were arbitrarily determined, aiming at a didactic presentation logic, for professionals and students who make this profession a mixture of art and science. Since dental practice in the current situation needs to be based on scientific evidence.

CHAPTER I

SYNDROMES OF DENTAL INTEREST: CORNELIA DE LANGE SYNDROME

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ABSTRACT

Cornelia de Lange Syndrome (CSdL), or Brachmann de Lange Syndrome, is a rare congenital anomaly, diagnosed through clinical and molecular examinations. A typical facial appearance, malformation of the upper limbs, delayed growth and development, impairment of the respiratory system, and psychomotor disability characterize SCdL. Changes in the maxilla and mandible result in dental problems due to poor tooth alignment. As patients also have intellectual disabilities and motor deficits, there is a favorable condition for the development of caries and periodontal diseases. People with the syndrome require monitoring by a multidisciplinary team. Each case must be planned individually, considering the limitations presented by the patient and to promote an improvement in their quality of life and health. Monitoring the patient after dental treatment is important to compensate for possible oral hygiene deficits.

Keywords: Cornelia de Lange Syndrome, dental treatment, dental problems, oral hygiene, feeding difficulties.

1. INTRODUCTION

Cornelia de Lange Syndrome (SCdL), or Brachmann de Lange Syndrome, is a rare congenital anomaly. The prevalence in newborns varies between 1/10,000 and 1/30,000 (Kline *et al*., 2018). It was first reported in 1849 by Vrolik, followed by Brachmann in 1916 (KINJO *et al*., 2019), and in 1933, Cornelia de Lange described in detail the cases of two children who presented mental deficiency and other clinical characteristics with milder manifestations, thus giving its name to the syndrome (DE Lima *et al*., 2017).

Different mutations are associated with SCdL and different combinations of these mutations lead to varied clinical manifestations, which can be classified as classic SCdL, and non-classical SCdL among other phenotypes with limited signs of the syndrome. Genes belonging to the cohesin protein complex are normally involved, namely NIPBL, SMC1A, SMC3, RAD21, BRD4, HDAC8, and ANKRD11. Mosaicism is also present in some individuals with the syndrome (Cascella; Muzio, 2020).

A risk of recurrence of 0.89% is estimated when the parents are healthy due to the possibility of gonadal mosaicism, when there is no possibility of molecular assessment the empirical risk is 1.5 (Kline *et al*., 2018).

2. CHARACTERISTICS OF THE SYNDROME

An SCdL is characterized by a typical facial appearance that presents synopsis (the main characteristic of the syndrome), low frontal hairline, low-set ears, and microstomia (Cascella; Muzio, 2020), the other most evident manifestations are malformation of the upper limbs, delayed growth and development, as well as psychomotor deficiency (França *et al*., 2009).

People with the syndrome also present dysfunctions of gastroesophageal, cardiac, ophthalmological, and genitourinary anomalies. Other diseases such as pyloric stenosis, congenital diaphragmatic hernia, cardiac septal defects, hearing loss, autism, and tendencies towards self-harm may be associated (Kline *et al*., 2018).

Among the oral characteristics are micrognathia, long philtrum, thin upper lip, high palate with cleft palate associated or not, microdontia, partial anodontia, delayed eruption, wide diastemas, enamel hypoplasia, narrowing of the dental arches, periodontal disease, bruxism and dental erosion due to reflux gastric (França *et al*., 2009; Kline *et al*., 2018).

3. DIAGNOSIS

In general, the diagnosis of SCdL is made based on clinical criteria, in the pre-or post-natal period, using genetic tests in a complementary way in cases where history analysis and physical examination are not sufficient to confirm the diagnosis (Kinjo *et al*., 2019; Cascella; Muzio, 2020;).

In 2018, a tool for diagnosing SCdL was created. The tool is based on the distinction between main characteristics and suggestive characteristics, with scores being assigned for each one.

Frame. Main and suggestive clinical characteristics for clinical evaluation and diagnosis of SCdL. Main features, suggestive features:

Main features	Suggestive features
• Sinophris or thick eyebrows • Short nose, concave nasal ridge or upturned nasal tip • Long and/or smooth philtrum • Redness of the thin upper lip and/or corners turned down • Oligodactyly and/or adactyly (congenital lack of fingers and hands) • Congenital diaphragmatic hernia	• Global developmental delay and/or intellectual disability • Prenatal growth retardation • Postnatal growth retardation • Microcephaly (prenatal and/or postnatal) • Small hands and/or feet • Short fifth finger • Hirsutism

The main characteristics present count 2 points and each suggestive characteristic present counts 1 point, so the diagnosis is given based on the final result: if the final score is ≥ 11 with at least 3 main characteristics, the diagnosis is indicative of classic SCdL; if it is 9 or 10 with at least 2 main characteristics, the diagnosis is suggestive of non-classical SCdL; if it is 4 to 8 points with at least 1 main characteristic, the molecular test is necessary to confirm the suspicion; and if the score is less than 4 there is not enough evidence to request further tests (Kline *et al*., 2018).

4. DENTAL TREATMENT

There is no specific treatment for SCdL, so those with the syndrome require monitoring by a multidisciplinary team, following an individualized clinical protocol, providing health and improving quality of life (França *et al*., 2009; Kline *et al*., 2018).

Feeding difficulties are present in almost all SCdL cases and among the factors that contribute to this limitation are cleft palate, micrognathia, and dental problems (Kline *et al*., 2018; Romano *et al*., 2017). Caries and periodontal disease are present in most of these patients and are aggravated by poor hygiene, resulting from an intellectual disability that makes it impossible to understand the importance of brushing and also due to motor deficit, which makes it difficult to perform the correct movements for effective oral cleaning (De-Lima *et al*., 2017).

Awareness of the importance of oral hygiene, as well as oral hygiene instructions, should be made to family members and caregivers in the initial phase of treatment, then topical fluoride applications and the planning of a healthy diet can be carried out together

with other professionals. After completing these steps, it is important to have periodic consultations to maintain oral health (Kline *et al*., 2018).

More invasive treatments can be made difficult by the lack of patient collaboration, making it necessary to use conditioning techniques to carry out procedures using local anesthesia, as reported by França *et al*., 2009, as well as sedation and general anesthesia can be secondary options in some cases (De-Lima *et al*., 2017).

Some care must be taken if general anesthesia is the chosen option, due to the respiratory problems present in these patients, such as very sensitive airways and susceptibility to bronchospasms, the difficulty in the intubation process, and the risk of cardiovascular complications (Moretto *et al*., 2016; Kachko *et al*., 2010;).

5. DISCUSSION

Combinations between variations in genes involved in SCdL lead to different phenotypes in individuals that can result in a classic case, non-classic case, and other phenotypes with limited signs of SCdL (Kline *et al*., 2018; Cascella; Muzio, 2020).

The diagnosis can be made pre- or post-natally, normally occurring post-natally due to the greater ease of observing clinical characteristics when compared to the pre-natal period with ultrasound. The clinical diagnosis considers the typical characteristics of the syndrome that may be evident or more subtle, and the diagnosis can also be complemented by molecular tests to detect changes in the genes of the cohesin complex (Kline *et al*., 2018; Kinjo *et al*., 2019;).

The treatment of these patients must be carried out by a multidisciplinary team (França *et al*., 2009; Sandhu *et al*., 2015). Patient conditioning is of paramount importance due to the need for patient contribution to carry out the procedures (Castilho; Piva; Guirardo,2000; De-Lima *et al*., 2017). In cases where this is not possible, it is possible to perform the procedures under general anesthesia or sedation (França *et al*, 2009; Sandhu *et al*, 2015).

Case planning must be done on an individual basis, considering the limitations presented by the patient and to promote improvements in their quality of life and health (De-Lima et al., 2017), and monitoring the patient after treatment is important to maintain their oral health (Kline *et al*., 2018).

6. CONCLUSION

SCdL has different forms of clinical manifestation with different genes involved, and due to its complexity, a multidisciplinary team is necessary to assist the patient. The treatment of these patients in dentistry requires knowledge about the possible changes to be encountered to determine the best way to proceed and offer a better quality of life and health.

REFERENCES

CASCELLA, M.; MUZIO, MR Cornelia de Lange Syndrome. In: StatPearls. Treasure Island (FL): StatPearls Publishing, 2020.

CASTILHO, JB; PIVA, GA; GUIRARDO, CG Cornelia and Lange syndrome: difficulties encountered regarding dental treatment. UFES Dental Magazine, v. 2, no. 1, p. 8–13, jun. 2000.

DE LIMA, AM et al. Lip frenectomy in a patient with Cornelia de Lange syndrome. Journal of Dentistry of the City of São Paulo University, v. 26, no. 2, p. 170, 28 Nov. 2017.

FRANCE, DCC et al. CLINICAL, MORPHOLOGICAL AND GENETIC CHARACTERISTICS OF CORNELIA DE LANGE SYNDROME. Araçatuba Dental Magazine, v. 30, no. 1, p. 55–58, jun. 2009.

KACHKO, L. et al. Spinal anesthesia in a child with Brachmann-de Lange (Cornelia de Lange) syndrome. Journal of Anesthesia, vol. 24, no. 6, p. 942–944, 1 Dec. 2010.

KINJO, T. et al. A Case of Cornelia de Lange Syndrome: Difficulty in Prenatal Diagnosis. Case reports in obstetrics and gynecology, vol. 2019, p. 4530491–4530491, May 13, 2019.

KLINE, AD et al. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. NatureReviews. Genetics, vol. 19, no. 10, p. 649–666, 2018.

MORETTO, A. et al. Sedation and general anesthesia for patients with Cornelia De Lange syndrome: A case series. American Journal of Medical Genetics Part C: Seminars in Medical Genetics, vol. 172, no. 2, p. 222–228, 2016.

ROMANO, C. et al. European Society for Pediatric Gastroenterology, Hepatology and Nutrition Guidelines for the Evaluation and Treatment of Gastrointestinal and Nutritional Complications in Children With Neurological Impairment.Journal of Pediatric Gastroenterology and Nutrition, v. 65, no. 2, p. 242–264, 2017.

SANDHU, M. et al. Dental management of cornelia de lange syndrome: a rare case report. Journal of clinical and diagnostic research: JCDR, v. 9, no. 2, p. ZD12–ZD14, Feb. 2015.

SCARPELLI, AC et al. Cornelia De Lange syndrome: a case report of a Brazilian boy. The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association, vol. 48, no. 4, p. 490–493, Jul. 2011.

CHAPTER II

SYNDROMES OF DENTAL INTEREST: MARFAN SYNDROME

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ABSTRACT

Marfan Syndrome (MFS) is a rare hereditary systemic disease of the connective tissue. It is considered a disease without gender, race, or color predisposition, and its estimated prevalence is 1/10,000. Most cases of MFS are due to mutations in the FBN1 gene located on chromosome 15q21, encoding fibrillin. Marfan Syndrome involves a variety of clinical manifestations in different tissues, especially in the ocular, musculoskeletal, and cardiovascular systems. Patients who are affected by Marfan Syndrome have many craniofacial abnormalities such as Class II dental and skeletal abnormalities with maxillary and mandibular retrognathia and dolichocephaly, as well as maxillary constriction with an increase in palatal depth and dental crowding. The prevalence of joint hypermobility is another common finding that leads to temporomandibular joint dysfunction (TMD) with possible condylar resorption. Physiotherapy should be one of the pillars of TMD therapy, this includes joint stabilization in patients at the beginning of each orthodontic treatment. Due to periodontal inflammation, professional cleaning is required at regular intervals to reduce inflammation and reduce the risk of endocarditis. Taking into account that cardiovascular changes are the most fatal, the dentist must be aware of the use of anesthetics and vasoconstrictors. Knowledge of the signs and symptoms of the syndrome is important, as, given the large number of oral and maxillofacial changes present, the dentist may be the first to raise suspicions about the case..

Keywords: Marfan syndrome, dental treatment, cardiovascular changes, periodontitis, temporomandibular dysfunction.

1. INTRODUCTION

Marfan Syndrome (MFS) is a rare hereditary systemic disease of the connective tissue that was described by Antoine Marfan in 1896 (Silva, 2016). Its estimated prevalence is 1/10,000 and there is no predisposition of gender, race or color (Achelrod *et al*., 2014). Patients with the syndrome, for the most part, inherit the disease through autosomal dominant genetic inheritance within the family (Achelrod *et al*., 2014), but around 20 to 30% of new cases of MFS in classic patients are the result of new mutations (Tognato *et al*., 2019).

In most cases, the mutation responsible for the syndrome is present in the FBN1 gene (Mannucci *et al*., 2020) located on chromosome 15q21, encoding fibrillin, which is a glycoprotein structural component of the elastic fibers of the extracellular matrix of connective tissue (Tognato *et al*., 2019). Its deficiency can compromise the tissue support function and the transforming growth factor/TGF-β regulation process (Silva, 2016).

2. CLINICAL MANIFESTATIONS

MFS involves a variety of clinical manifestations that can often be explained by associated connective tissue dysfunction, especially involving the ocular, musculoskeletal and cardiovascular systems (El-Ouali *et al*., 2020). Among the ocular manifestations are ectopic lens, flat cornea, increased axial length of the globe and hypoplastic iris (Esfandiari *et al*., 2019; Vanem *et al*., 2019).

Musculoskeletal changes are the most frequent and striking (Baraldi; De-Paris; Robinson, 2010) such as tall stature, arachnodactyly, anterior chest wall deformity, mild to moderate joint laxity and spinal deformity, especially scoliosis (Lin *et al*., 2020).

Cardiovascular changes are those that most threaten the lives of these patients, due to the possibility of dissection and rupture of the aorta (Vanem *et al*., 2019; Van Camp; Aerden; Politis, 2020). Presence of aortic root dilation varies from 62 to 88% of cases, mitral valve prolapse in up to 90% and pulmonary artery dilation in 54 to 74%, sand that mitral valve prolapse can progress to severe valve insufficiency or infective endocarditis (Achelrod *et al*., 2014; Vanem *et al*., 2019).

Physically, children with this syndrome appear older than their chronological age and half of them present neuropsychic changes, including learning difficulties, attention deficit and impaired verbal communication (Silva, 2016).

3.DIAGNOSIS

The diagnosis of this disease is made based on clinical criteria described in the Ghent nosology, these criteria were revised in 2010 based on a critical review of the clinical characteristics reported in studies with a large number of patients and with the opinion of experts with extensive experience in the field. use of the criteria, resulting in the revised Ghent nosology (Loeys *et al*., 2010; Vanem *et al*., 2019).

The main clinical features determined by the revised Ghent criteria are aortic root dilation and ectopic lens. The presence of these findings, even in the absence of family history, is sufficient to confirm the diagnosis. In cases where one of the two is not present, FBN1 testing or a combination of systemic manifestations is necessary to confirm the diagnosis. The assessment of systemic manifestations is made using a scoring system (Loeys *et al*., 2010)

Legend. Scoring of systemic manifestations.

Systemic Manifestation	Punctuation
• Wrist and thumb sign	3
• Wrist or thumb sign	1
• Pectus carinatum	two
• Pectus excavatum	1
• Chest Asymmetry	1
• Rearfoot	two
• Flat foot	1
• Pneumothorax	two
• Dural ectasia	two
• Protrusium acetabuli	two
• Reduced upper/lower segment ratio	1
• Increased height or arm	1
• Non-severe scoliosis	1
• Scoliosis or thoracolumbar kyphosis	1
• Reduced elbow extension	1
• Facial features (3/5) (dolichocephaly, enophthalmos, downward-sloping palpebral fissures, malar hypoplasia, retrognathia)	1
• Stretch marks on the skin	1
• Myopia > 3 diopters	1
• Mitral valve prolapse	1
Score >= 7 indicates systemic involvement.	

4.TREATMENT

As there is no cure, treatment is directed at the systems affected by the syndrome. In the case of cardiological changes, treatments include drug therapy with the use of beta-blockers, withdrawal from intense sports, repair of the mitral valve or implantation of a mechanical mitral valve and prophylactic surgery of the ascending portion of the aorta (Loeys *et al*., 2010; Achelrod *et al*., 2014;).

Open thoracic aortic surgery has been the gold standard for the treatment of aortic dilations and dissections (Pellenc *et al*., 2020). Surgical repair or replacement of the mitral valve is recommended when there is prolapse, repair procedures are superior to replacement in the long term (Polanco *et al*., 2019).

Annual ophthalmological evaluation should be carried out in order to early detect lens subluxation, cataracts, glaucoma and retinal detachment. These complications can be resolved through surgical procedures, the use of glasses or contact lenses (Esfandiari *et al*., 2019).

The treatment of skeletal deformities such as scoliosis can be performed through surgical procedures (Palmisani *et al*., 2019).

5. DENTAL TREATMENT

Individuals who are affected by MFS have several craniofacial abnormalities such as dental and skeletal class II with maxillary and mandibular retrognathia, dolichofacial profile, as well as maxillary constriction with increased palatal depth and dental crowding (Van Camp; Aerden; Politis, 2020).

During the growth phase, orthodontic and facial orthopedic treatment should be used with the aim of correcting patients' malocclusion and managing craniofacial growth in the best possible way, with special emphasis on functional appliances (Von-Kodolitsch *et al*., 2016).

The prevalence of joint hypermobility is another common finding that can lead to temporomandibular joint dysfunction (TMD), including the possibility of osteoarthritis that leads to condylar resorption. Pain during mouth opening, "clicks" when opening and/or closing the mouth and subluxation symptoms that include joint pain, exaggerated mouth opening with discomfort and the possibility of open locking, are important complaints to address in relation to TMD. Furthermore, imaging findings frequently reveal anterior displacement of the articular disc, and in severe cases, condylar resorption due to the development of osteoarthrosis (Bauss *et al*., 2004; Von-Kodolitsch *et al*., 2016).

Periodontitis conditions need to be treated through prophylaxis and scaling of dental elements at regular intervals with the aim of reducing inflammation and consequently reducing the risk of endocarditis (Silva, 2016). In cases of periodontitis that led to edentulism, implant prostheses are not contraindicated, representing a good rehabilitative option (Kutkut *et al*., 2020). Patients may also present with muscular hypotonia that results in reduced lip strength, increased lower facial height, reduced chewing efficiency and altered craniofacial morphology. In these cases, myofunctional therapy presents itself as an option to achieve lip competence and strengthen orofacial muscles during the growth period (Von-Kodolitsch *et al*., 2016).

When there is a need to perform more invasive procedures, the use of local anesthetics containing adrenergic vasoconstrictors must be done with caution, due to cardiovascular changes, non-adrenergic vasoconstrictors such as prilocaine and levonordefrin can be used as an alternative, as well as anesthetic solutions without vasoconstrictors (Baraldi; De-Paris;

Robinson, 2010), among the anesthetic solutions, mepivacaine 3% is the most chosen (Van Camp; Aerden; Politis, 2020).

Sessions should be kept to a minimum, causing as little stress as possible to the patient, and blood pressure and heart rate should be monitored throughout the procedure (Baraldi; De-Paris; Robinson, 2010). In cases where very extensive procedures will be performed or manipulation of regions with inflammation or infection, antibiotic prophylaxis is recommended, but only in patients with a history of bacterial endocarditis or who have a cardiac prosthesis (Wilson *et al*., 2007; ARAÚJO *et al*., 2016).

6. DISCUSSION

MFS involves a variety of clinical manifestations in different tissues (El-Ouali *et al*., 2020), the dental surgeon deals mainly with musculoskeletal and cardiovascular changes. Among local anesthetics, mepivacaine 3% appears as the preferred choice in dental procedures. (Van-Camp; Aerden; Politis, 2020), in the case of vasoconstrictors, prilocaine and levonordefrin are more indicated because they are non-adrenergic (Baraldi; De-Paris; Robinson, 2010), in the case of very extensive dental treatments in which several applications of local anesthetic would be necessary, it is best to use sedation or general anesthesia (Van-Camp; Aerden; Politis, 2020). In the perioperative period, beta-blockers can be used to reduce tension in the aortic wall during procedures (Araújo *et al*., 2016).

In the case of TMD, treatment to stabilize joint function must be carried out in association with physiotherapy and the treatment of muscular hypotonia can be carried out through myofunctional therapy, which aims to strengthen the facial muscles. During the growth phase, orthodontic treatment can be carried out using functional appliances and thus lead to better craniofacial development of the patient (Von-Kodolitsch *et al*., 2019).

7.CONCLUSION

The identification of patients with MFS and the determination of compromised organs and/or systems before dental treatment are important so that the dentist can take the necessary care during the service and can offer the best possible treatment, promoting a better quality of life. . Knowledge of the signs and symptoms of the syndrome is important because given the large number of oral and maxillofacial changes present, the dentist may be the first to raise suspicions about the case.

REFERENCES

ACHELROD, D. *et al*. The economic impact of Marfan syndrome: a non-experimental, retrospective, population-based matched cohort study. Orphanet journal of rare diseases, v. 9, p. 90–90, 23 June. 2014.

ARAÚJO, MR *et al*. Marfan syndrome: new diagnostic criteria, same anesthetic approach? Case report and review. Brazilian Journal of Anesthesiology, v. 66, no. 4, p. 408–413, Jul. 2016.

ARSLAN-KIRCHNER, M.; VON KODOLITSCH, Y.; SCHMIDTKE, J. The Importance of Genetic Testing in the Clinical Management of Patients with Marfan Syndrome and Related Disorders. Deutsches Ärzteblatt International, v. 105, no. 27, p. 483–491, Jul. 2008.

BARALDI, CE; DE PARIS, MF; ROBINSON, WM Marfan Syndrome and its dental aspects: literature review. Magazine of the Faculty of Dentistry of Porto Alegre, v. 49, no. 3, p. 36–39, 6 May 2010.

BAUSS, O. *et al*. Temporomandibular joint dysfunction in Marfan syndrome. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, vol. 97, no. 5, p. 592–598, May 2004.

DE MAIO, F. *et al*. Orthopedic Aspects of Marfan Syndrome: The Experience of a Referral Center for Diagnosis of Rare Diseases. Advances in Orthopedics, vol. 2016, 2016.

EL OUALI, Z. *et al*. Pneumothorax spontané recidivant révélant un syndrome de Marfan. Revue des Maladies Respiratoires, v. 37, no. 1, p. 86–90, Jan. 2020.

ESFANDIARI, H. *et al*. Management Strategies of Ocular Abnormalities in Patients with Marfan Syndrome: Current Perspective. Journal of ophthalmic & vision research, vol. 14, no. 1, p. 71–77, 2019.

LIN, M. *et al*. Genetic and molecular mechanism for distinct clinical phenotypes conveyed by allelic truncating mutations implicated in FBN1. Molecular genetics & genomic medicine, vol. 8, no. 1, p. e1023–e1023, Jan. 2020.

LOEYS, BL *et al*. The revised Ghent nosology for the Marfan syndrome. Journal of Medical Genetics, vol. 47, no. 7, p. 476–485, 30 June. 2010.

MANNUCCI, L. *et al*. Mutation analysis of the FBN1 gene in a cohort of patients with Marfan Syndrome: A 10-year single center experience.Clinica Chimica Acta, v. 501, p. 154–164, Feb. 2020.

PALMISANI, M. *et al*. Surgical treatment of spinal deformities in Marfan syndrome: Long--term follow-up results using different instrumentations. Journal of craniovertebral junction & spine, vol. 10, no. 3, p. 172–178, 2019.

PELLENC, Q. *et al*. Optimizing Aortic Endovascular Repair in Patients with Marfan Syndrome. European Journal of Vascular and Endovascular Surgery, vol. 59, n. 4, p. 577–585, apr. 2020.

POLANCO, AR *et al*. Institutional Marfan syndrome surgical volume influences mitral valve surgical strategy in patients with Marfan syndrome. Journal of Cardiac Surgery, vol. 34, no. 12, p. 1533–1539, 15 Oct. 2019.

SILVA, RT DA. Knowledge about Marfan syndrome: contributions to the creation and validation of an assessment instrument. Knowledge about Marfan syndrome: contributions to the creation and validation of an assessment instrument. Anais... In: KNOWLEDGE ABOUT MARFAN SYNDROME: CONTRIBUTIONS TO THE CREATION AND VALIDATION OF AN ASSESSMENT INSTRUMENT. FEUC, 29 September. 2016Available at: <https://estudogeral.sib.uc.pt/handle/10316/33223>. Accessed on: 19 April. 2020

TOGNATO, E. *et al*. Neonatal Marfan Syndrome. American Journal of Perinatology, vol. 36, no. S 02, p. S74–S76, 25 Jun. 2019.

VAN CAMP, N.; AERDEN, T.; POLITIS, C. Problems in the orofacial region associated with Ehlers-Danlos and Marfan syndromes: a case series. British Journal of Oral and Maxillofacial Surgery, vol. 58, no. 2, p. 208–213, Feb. 2020.

VANEM, TT *et al*. Marfan syndrome: Evolving organ manifestations—A 10-year follow-up study.American Journal of Medical Genetics Part A, vol. 182, no. 2, p. 397–408, 11 Dec. 2019.

VENZA, N. *et al*. Periodontal condition in growing subjects with Marfan Syndrome: a case--control study. PeerJ, v. 7, 2019.

VON KODOLITSCH, Y. *et al*. The role of the multidisciplinary health care team in the management of patients with Marfan syndrome.Journal of multidisciplinary healthcare, v. 9, p. 587–614, 3 Nov. 2016.

VON KODOLITSCH, Y. *et al*. Features of Marfan syndrome not listed in the Ghent nosology – the dark side of the disease. Expert Review of Cardiovascular Therapy, vol. 17, no. 12, p. 883–915, 2 Dec. 2019.

WILSON, W. *et al*. Prevention of infectious endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation, vol. 116, no. 15, p. 1736–1754, 9 Oct. 2007.

CHAPTER III

SYNDROMES OF DENTAL INTEREST: MOEBIUS SYNDROME

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ABSTRACT

Moebius Syndrome is reported to be a rare occurrence with an estimated incidence of 1:10,000 to 1:50,000 live births. The basic diagnostic criterion would be a congenital, non-progressive, non-expressive face with limited abduction of one or both eyes. Orthodontic treatment can be carried out during the growth phase to direct adequate growth of the maxilla and reduce malocclusion, as well as prophylactic treatments, hygiene instructions, and application of fluoride must be carried out due to greater susceptibility to carious lesions. More invasive treatments such as endodontic treatment, extractions, and orthognathic surgery generate more difficulties due to the limitations presented by patients, such as limited mouth opening when using handpieces and instruments. Prior knowledge of the clinical manifestations of the syndrome is necessary to provide early approaches and adequate dental follow-up.

Keywords: Moebius syndrome, Mask face, Malocclusion, Prophylactic treatment, Orthodontic treatment.

1. INTRODUCTION

Moebius Syndrome (MS) was first described in 1880 by Von Graaefe through a case report of a patient with facial nerve paralysis, between 1888 and 1892, by Paul Moebius, characterizing an individual with congenital bilateral facial weakness, pectoral muscle malformation, syndactyly and absence of eye abduction (Brasileiro *et al*., 2012; Cudzilo; Matthews-Brzozowska, 2019).

Also known as Moebius/Mobius Sequence or Congenital Facial Dysplegia, it is reported to be a rare occurrence with an estimated incidence of 1:10,000 to 1:50,000 live births (Fernandes *et al*., 2015). The patient presents unilateral or bilateral congenital facial paralysis and involvement of the abducens and facial nerves, with or without changes in the other cranial nerves and malformations throughout the body (Magnifico *et al*., 2017). The pathophysiological mechanisms begin in the embryonic phase and their manifestations extend throughout the individual's growth (Brasileiro *et al*., 2012).

2. CLINICAL FEATURES

The two main features are facial nerve paralysis, causing the so-called "mask face" and abducens (Bell *et al*., 2019). Among the most common orofacial changes are bifid uvula, cleft palate, micrognathia, high palate, small lips with reduced mobility, incomplete lip

sealing, presence of sialorrhea, cheeks with altered tone and mobility, hypertonic mental portion, tongue with grooves, asymmetry, decreased mobility and fasciculations, microglossia and ankyloglossia (Sordi *et al*., 2014; Magnifico *et al*., 2017; Cudzilo; Matthews-Brzozowska, 2019). The temporomandibular joint can present varying degrees of degeneration with generally bilateral involvement and hyper- or hypomobility of the condyle, which can lead to a reduction in maximum opening, protrusion, and laterality movements (Magnifico *et al*., 2017).

In the ocular region, there may strabismus, eyelid ptosis, epicanthic folds, hypertelorism, absence of eyelid reflex, and pupillary reaction to light, the ear region may present macro or microtia and calciform ears. The absence of acoustic reflexes is a consequence of facial nerve paralysis (Sordi *et al*., 2014).

The extremities may suffer changes such as congenital clubfoot, polydactyly, syndactyly, and arthrogryposis (Guedes, 2014). Cardiovascular changes are rare, including dextrocardium, interatrial or ventricular communication, transposition of large blood vessels, and total anomalous pulmonary venous connection (Magnifico *et al*., 2017).

Occasionally other pairs of cranial nerves may be affected, difficulty chewing, swallowing and coughing are due to paralysis in nerves V, X, XI, and XII, if the VIII pair is affected there will be complications in hearing and speech. Due to limitations in facial expression, the patient may be wrongly diagnosed with mental retardation. It is estimated that 10 to 15% of cases truly present this condition. Autism conditions often appear related to the syndrome (Pradhan; Gryst, 2015).

3. DIAGNOSIS

The rarity and variety of clinical manifestations of the syndrome make its diagnosis difficult. The basic diagnostic criteria would be a non-expressive, congenital, non-progressive face with limited abduction of one or both eyes (Bell *et al*., 2019). Soon after birth, it is possible to observe some signs such as incomplete closure of the eyelids during sleep and constant drooling (Pradhan; Gryst, 2015).

4. DENTAL TREATMENT

The treatment of patients with MS is carried out by a team of specialists, and as there is no cure for the syndrome, the focus is on the changes present (Mahrous; Thalji, 2018).

Initially, dysphagia and aspiration are the problems that pose the greatest risk to patient's lives, so the use of feeding tubes in babies and the implementation of special diets

help with this problem and guarantee the necessary nutrition. During the growth phase, early orthodontic treatment must be carried out to expand the upper dental arch and thus correct the malocclusion present in cases of high palate, which is important to reduce the chances of needing orthognathic surgery in adulthood (Pradhan; Gryst, 2015).

In cases where orthognathic surgery is necessary, prior treatment of facial paralysis must be carried out to prevent lip deformities. Currently, the gold standard for facial animation treatment is smile surgery, but in cases where the paralysis is partial. Speech therapy and physical therapy can produce satisfactory results. Treatment for facial paralysis should be carried out as early as possible to reduce psychological consequences and improve interpersonal relationships and the patient's psychophysical development (Magnifico *et al*., 2017).

Patients with MS have a greater chance of developing cavities, as with the reduction in muscle activity in the lips, leading to incomplete sealing of the lips, tongue, and cheek, a diet with soft or even pasty foods ends up being a natural choice for them, which ends up favoring food retention. With this in mind, it is important to carry out preventive treatment in these patients through prophylaxis, oral hygiene instructions, and application of fluoride (Castro *et al*., 2016; Pradhan; Gryst, 2015).

In cases where restorative treatment is necessary, the main difficulties encountered are related to limited mouth opening. During procedures, it becomes difficult to obtain adequate lighting and use handpieces and instruments; the atraumatic restorative technique is an alternative for treating these cases. In more invasive procedures requiring intraoral anesthesia, it is often associated with general anesthesia, however, there are risks due to the difficulty in intubating the patient and possible aspiration during the procedure (Pradhan; Gryst, 2015).

In patients where there is a need for prosthetic rehabilitation, limited mouth opening, changes in speech, and compromised neuromuscular activity are the biggest complications of treatment, as shown in the case of Mahrous and Tajhli (2018), where it was necessary to remove part of the edge of the complete implant prosthesis to reduce the material until adequate lip sealing was possible (Mahrous; Thalji, 2018).

5. DISCUSSION

Orthopedic treatment should be preferred in correcting malocclusions, taking advantage of the growth phase to direct adequate growth of the maxilla and improve skeletal conditions since muscle opening and functioning are inadequate in this development

(Pradhan; Gryst, 2015). Prophylactic treatments, hygiene instructions, and application of fluoride must be carried out with greater emphasis due to greater susceptibility to carious lesions through the common diet choice of these patients and food retention (Castro *et al*., 2016; Cudzilo; Matthews-Brzozowska, 2019).

When preventive treatment is not carried out, other more invasive treatments such as endodontic treatment, extractions, and surgeryorthognathic surgery may be necessary and generate more difficulties due to the limitations presented by the patient (Castro *et al*., 2016; Pradhan; Gryst, 2015). The use of local anesthetics is often essential and their use faces the same problems as the use of handpieces and instruments, general anesthesia then appears as an alternative, although there are also problems such as perioperative aspiration (Pradhan; Gryst, 2015). Even prosthetic treatment requires adaptations due to the patient's limitations (Mahrous; Thalji, 2018), therefore acting preventively appears as the best option to be followed, emphasizing oral health education.

6. CONCLUSION

The changes in the cranial nerve pairs present in patients with SM have a direct impact on their oral health and prophylactic treatment in response to greater susceptibility to carious lesions and orthodontic treatment or orthognathic surgery to correct the occlusion are the surgeon's main work fronts. dentist in these frames. Prior knowledge of the clinical manifestations of the syndrome is necessary to provide the best possible results and thus improve patients' quality of life.

REFERENCES

BELL, C. *et al*. Will the real Moebius syndrome please stand up? A systematic review of the literature and statistical cluster analysis of clinical features. American Journal of Medical Genetics Part A, vol. 179, no. 2, p. 257–265, 2019.

BRASILEIRO, I. DE C. *et al*. Möbius Syndrome: characterization of children treated in an institution in Fortaleza-CE. Brazilian Journal on Health Promotion, v. 25, no. 1, p. 37–44, 30 Mar. 2012.

CASTRO, T. *et al*. Caries Experience in Individuals with Moebius Syndrome. Pediatric Dentistry, vol. 38, no. 1, p. 68–71, Feb. 2016.

CUDZILO, D.; MATTHEWS-BRZOZOWSKA, T. Moebius syndrome: The challenge of dental management. European Journal of Pediatric Dentistry, v. 20, no. 2, p. 143–146, jun. 2019.

FERNANDES, SD *et al*. Mõbius syndrome: meanings in the lives of sufferers. Rev. Soc. Bras. Clin. Med, 2015.

GUEDES, ZCF Möbius Syndrome: Misoprostol Use and Speech and Language Characteristics. International Archives of Otorhinolaryngology, vol. 18, no. 3, p. 239–243, Jul. 2014.

MAGNIFICO, M. *et al*. Pre- and Postsurgical Orthodontics in Patients with Moebius Syndrome. Case reports in Dentistry, vol. 2017, p. 1484065–1484065, 2017.

MAHROUS, A.; THALJI, G. Prosthodontic Management of a Patient with Moebius Syndrome: A Clinical Report. Journal of Prosthodontics: Official Journal of the American College of Prosthodontists, vol. 27, no. 3, p. 299–305, mar. 2018.

PRADHAN, A.; GRYST, M. Atraumatic restorative technique: case report on dental management of a patient with Moebius syndrome. Australian Dental Journal, vol. 60, n. 2, p. 255–259, jun. 2015.

SORDI, C. *et al*. Interdisciplinary work on the Möebius Sequence. [sl] Editora Plena, 2014.

CHAPTER IV

SYNDROMES OF DENTAL INTEREST: CROUZON AND APERT SYNDORMS

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ABSTRACT

Crouzon Syndrome is considered a syndromic craniosynostosis characterized by a premature fusion of the upper and posterior maxillary sutures along the orbit wall. Apert Syndrome is also syndromic craniosynostosis, characterized by premature fusion of bilateral coronary sutures and symmetrical syndactyly of the hands and feet. The prognosis of patients with craniosynostosis depends on early diagnosis and treatment, to enable interventions to improve craniofacial growth and development, minimize syndromic changes and deleterious conditions, and increase therapeutic possibilities. The corrective treatment of midfacial hypoplasia improves exophthalmos and dental occlusion and may combine orthodontic and orthopedic treatment and/or orthognathic surgery.

Keywords: Craniosynostosis, Crouzon Syndrome, Apert Syndrome, Midfacial hypoplasia.

1. INTRODUCTION

Craniosynostosis represents one of the most common congenital malformations affecting the human skull. Among syndromic craniosynostosis, Crouzon syndrome (CS) has the highest frequency. Its incidence is estimated at 4:100,000 people in the general population, while its frequency varies from 4.5% to 4.8% of all craniosynostosis (Maspero *et al*., 2014). The incidence of Apert syndrome (AS) is estimated at 1:100,000 live births, and the estimate is that it corresponds to 40% of cases of syndromic craniosynostosis (Azoulay--Avinoam *et al*., 2020).

CS is also characterized by premature fusion of the superior and posterior sutures of the maxilla along the orbital wall and its severity varies from patient to patient (Maspero *et al*., 2014). AS is characterized by premature fusion of bilateral coronal sutures and symmetrical syndactyly of the hands and feet (Kobayashi *et al*., 2020). Both are autosomal dominant hereditary diseases, although up to 50% of CS cases are new mutations caused by mutations in the fibroblast growth factor receptor 2 (FGFR2) gene (Kobayashi *et al*., 2020; Maspero *et al*., 2014). The FGF-2 defect also affects the respiratory, nervous, and musculoskeletal systems, which can lead to bilateral facial paralysis, exophthalmos, shallow orbits, divergent strabismus and optic nerve degeneration, iris fissures, lens dislocation, and glaucoma (Pawlicki *et al*., 2008).

These two syndromes have several common characteristics such as mid-facial deficiency, ocular proptosis, and hypertelorism, however, some craniofacial morphologi-

cal analyses are different, in general, patients with AS have a more abnormal craniofacial morphology than patients with CS (Kobayashi *et al*., 2020; Kreiborg; Cohen, 1998).

2. ADDITIONAL CHARACTERISTICS OF THE SYNDROMES

Patients with CS may present with a mild form of the disease, which allows them to lead a fully functional lifestyle, or a more severe form of the disease, which is associated with neurological, respiratory, and psychosocial disorders, as well as aesthetic problems (Helman *et al*., 2014; Khominsky *et al*., 2018). Typically, patients present with bicoronal synostosis, brachycephaly, shallow orbits with ocular proptosis, hypertelorism, midface hypoplasia and relative mandibular prognathism, nose with a parrot's beak, short and retracted upper lip and dental malocclusion (Stavropoulos *et al*., 2011; Conrady; Patel, 2021).

The widened forehead and shallow orbits are related to the pattern of the base of the anterior cranial fossa, which is widened and anteroposterior in length. shortened. These deformities persist over time and are progressive, which worsens the deficiency of the midface during growth (Lu *et al*., 2019a). Patients with AS have similar characteristics to CS, but the hypoplasia of the midface is more severe, which limits the nasopharyngeal air space and the oropharynx more, and they present syndactyly of the fingers and toes. Another distinguishing feature in people with AS is the presence of bilateral bulbous palatal enlargement that gives the appearance of a pseudocleft. (Azoulay-Avinoam *et al*., 2020). In both syndromes, cleft lip and/or palate, bifid uvula, and hearing loss may also be present (Maspero *et al*., 2014; Conrady; Patel, 2021;).

Concerning dentition and occlusion, those with CS show a maxillary deficiency in the vertical, transverse, and sagittal dimensions, generally present an anterior open bite, posterior and anterior crossbite, severe crowding of the upper arch, delayed tooth eruption, which is less severe than in SA, multiple supernumerary teeth and an increase in interdental spaces. In AS there is a delay of 1 to 2 years in dental development and consequent late eruption of teeth, crowding of the upper teeth, and the skeletal discrepancy between the maxilla and mandible, which leads to several of the problems previously described in SC (Pawlicki *et al*., 2008; Reitsma et al., 2014b; Torun; Akbulut, 2017; Azoulay-Avinoam *et al*., 2020). Dental agenesis is present in both but is more prevalent in patients with AS than in patients with SC, so its presence in both cases suggests common molecular mechanisms in dental and organic development (Reitsma *et al*., 2014a).

The mandible of patients with CS may present sagittal mandibular hypoplasia (shortened mandibular width and length and reduced height), the presence of bifid

mandibular condyles, expansive bone lesions, and dental changes. These developmental changes suggest that the changes go beyond the effects resulting from sutural fusion (Khominsky *et al*., 2018; Lu et al., 2019b). Fluctuating asymmetry, which is used as an indicator of developmental instability, is greater in patients with AS than with SC. This occurs due to the influence of genetic and environmental factors, such as stress, and surgical and medical interventions (Elmi *et al*., 2015).

3. DIAGNOSIS

Crouzon syndrome is commonly diagnosed during childhood, with the initial and most critical aspect of the diagnosis being the clinical aspect of midfacial hypoplasia and exophthalmos (Helman *et al*., 2014). An experienced sonographer or obstetrician can also detect early evidence of cranial suture fusion during ultrasound or detailed 3D scanning procedures (Hariri *et al*., 2018). However, in cases where there is a spontaneous mutation the clinical presentation is unclear.

In multiple syndromic craniosynostosis have a defect in one of the FGFRs, so there is some overlap in their molecular pathophysiology (Conrady; Patel, 2021). Differential diagnosis from other syndromic craniosynostosis is important, for example, Apert syndrome is distinct because of its characteristic symmetrical syndactyly of the hands and feet; Pfeiffer syndrome is known for patients with wide thumbs and big toes having valgus deformity; Saethre-Chotzen syndrome does not have Apert's syndactylic feature or Crouzon's proptosis, it has a low frontal hairline, parrot-beaked nose, brachydactyly and milder bone deformities (Helman *et al*., 2014).

4. TREATMENT

The prognosis of patients with craniosynostosis depends on early diagnosis and treatment, and from this, it is possible to guide craniofacial growth and development, minimize changes, and increase the chances of reducing deleterious syndromic changes (Maspero *et al*., 2014; Conrady; Patel, 2021;). Treatment needs to be personalized and comprehensive, which requires corroboration from several areas such as pediatric otorhinolaryngology, neurosurgery, plastic surgery, ophthalmology, pediatrics, speech therapy, audiology, social work, dentistry, and/or maxillofacial surgery (Helman *et al*., 2014).

In cases of severe CS, patients may present important functional disorders such as increased intracranial pressure, severe exorcism with the inability to close the eyelid, and severe upper airway obstruction with progressive obstructive sleep apnea because

of a severely hypoplastic maxilla. The extent of surgical treatment will depend on their age and how functionally and severely the patients are affected and can be carried out in separate stages or combined procedures. In pediatric patients, the indication for each major surgery must be agreed upon by members of the craniofacial team, as the procedure carries substantial risks of mortality and morbidity (Hariri *et al*., 2018).

Over the years, conventional craniofacial surgical techniques such as strip craniectomy, frontal-orbital advancement, and Le Fort III procedures have proven to be reliable in the treatment of syndromic craniosynostosis. However, there are some disadvantages, including prolonged operative time, considerable blood loss, and, occasionally, cerebrospinal leakage. In severe cases, large segmental advancement requires the bone gap to be grafted, stabilized, and closed due to the resistance of the soft tissues (Hariri *et al*., 2018; Helman *et al*., 2014). The introduction of distraction osteogenesis (DO) in craniofacial surgery has provided a reliable surgical alternative to achieve superior segmental advancement compared to conventional techniques (Hariri *et al*., 2018).

A Le Fort III with DO is currently the treatment of choice for severe cases of Crouzon and Apert syndrome, as it leads to the generation of bone and stretching of the surrounding soft tissues (Reitsma *et al*., 2013b). The benefits of OD compared to conventional surgery include the absence of donor site morbidity, the absence of post-surgical bone defects and the need for bone grafts, less intraoperative bleeding, the possibility of increasing soft tissue volume, and the possibility of obtaining larger corrections and best (Hariri *et al*., 2018; Reitsma *et al*., 2013b).

Complications of OD include infection, device externalization, scar formation, dislocation, device alteration, and fracture of the tethering bone structure (Helman *et al*., 2014). DOs with limited osteotomy have already been performed successfully, and more recently it has been proposed to perform sutural distraction of the midface without osteotomy in young patients, using the natural elasticity and remodeling capabilities of the midface suture and bone, which are preserved, reducing complications related to surgery (Tong *et al*., 2017).

The most widely used orthodontic treatment involves maxillary expansion, a solution to severely contracted maxillary arches that create posterior crossbites and incompatible arch shapes. The shape of the upper arch must be established early to minimize facial asymmetry and eliminate traumatic occlusion. For patients after adolescence, the palatal suture fuses creating considerable resistance of the circummaxillary sutures to maxillary

expansion; in such situations, surgically assisted maxillary expansion may be necessary (Azoulay-Avinoam *et al*., 2020).

An earlier approach allows for greater non-surgical dental resolutions through a combination of orthopedic and orthodontic treatment, seeking broader objectives in maxillo-mandibular skeletal harmonization. Devices such as the rapid maxillary expansion face mask can allow relative horizontal advancement and vertical lengthening of the midface and transverse augmentation of the maxilla. To achieve this, the head circumference must be within normal parameters, intracranial pressure within limits that do not cause hydrocephalus, and normal mental development (Maspero *et al*., 2014).

5. DISCUSSION

Craniosynostosis represents one of the most common congenital malformations that affects the human skull (Maspero *et al*., 2014). The initial and most critical aspect of its diagnosis is midfacial hypoplasia and exophthalmos (Helman *et al*., 2014), the sooner the diagnosis is made, the better the patient's prognosis will be (Conrady; Patel, 2021).

Ocorrective treatment of midfacial hypoplasia improves exophthalmos and dental occlusion (Helman *et al*., 2014), and it can be done with a combination of orthodontic and orthopedic treatment or through a surgical procedure, usually Le Fort III with DO (Reitsma *et al*., 2013b; Maspero *et al*., 2014).

Orthopedic and orthodontic treatment is effective in improving appearance and occlusion in milder cases (Maspero *et al*., 2014), where the expansion of the maxilla to reestablish the shape of the upper arch and thus minimize facial asymmetry and eliminate traumatic occlusion is the first stage of treatment. During the treatment, the positioning of the teeth is corrected, at this stage, as the sequence of tooth eruption in AS and SC is changed (Pawlicki *et al*., 2008; Azoulay-Avinoam *et al*., 2020). It is necessary to have specific knowledge of the sequence of tooth eruption of these patients in the mixed dentition phase (Reitsma *et al*., 2013a). Already in adolescence, with the fusion of the palatal suture at the end, it is often necessary to combine orthodontic treatment and orthognathic surgery (Azoulay-Avinoam *et al*., 2020).

In cases in severe cases, patients may present functional disorders that require surgery. The extent of the procedure will depend on the age and severity of the patient's clinical condition. Currently, DO is the most used technique as it has a series of benefits compared to conventional surgical procedures, enabling greater and better corrections (Reitsma *et al*., 2013b; Hariri *et al*., 2018;), as the technique improves, procedures tend to

become less and less invasive, leading to surgical planning without osteotomy (Tong *et al*., 2017).

6. CONCLUSION

Early diagnosis is the first step towards adequate treatment of both syndromic craniosynostosis discussed in this text. After diagnosis, the treatment plan must be created by a multidisciplinary team, taking into account the severity of each case. In the most serious cases, surgical procedures must be carefully planned, especially in pediatric patients, due to the risks inherent to the procedure.

REFERENCES

AZOULAY-AVINOAM, S. *et al*. An Overview of Craniosynostosis Craniofacial Syndromes for Combined Orthodontic and Surgical Management. Oral and Maxillofacial Surgery Clinics of North America, vol. 32, no. 2, p. 233–247, May 2020.

CONRADY, CD; PATEL, BC Crouzon Syndrome. In: StatPearls. Treasure Island (FL): StatPearls Publishing, 2021.

ELMI, P. *et al*. Mandibular asymmetry in patients with the crouzon or Apert syndrome. The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association, vol. 52, no. 3, p. 327–335, 2015.

HARIRI, F. *et al*. Crouzon Syndrome: A Case Series of Craniomaxillofacial Distraction Osteogenesis for Functional Rehabilitation. Journal of Oral and Maxillofacial Surgery: Official Journal of the American Association of Oral and Maxillofacial Surgeons, vol. 76, no. 3, p. 646.e1-646.e12, 2018.

HELMAN, S. et al. Revisiting Crouzon syndrome: reviewing the background and management of a multifaceted disease. Oral and maxillofacial surgery, v. 18, no. 4, Dec. 2014.

KHOMINSKY, A. *et al*. Extensive phenotyping of the orofacial and dental complex in Crouzon syndrome. Archives of Oral Biology, vol. 86, p. 123–130, Feb. 2018.

KOBAYASHI, Y. *et al*. Craniofacial, oral, and cervical morphological characteristics in Japanese patients with Apert syndrome or Crouzon syndrome. European Journal of Orthodontics, 7 March. 2020.

KREIBORG, S.; COHEN, MM Is craniofacial morphology in Apert and Crouzon syndromes the same? Acta Odontologica Scandinavica, v. 56, n. 6, p. 339–341, Dec. 1998.

LETRA, A. *et al*. Intraoral characteristics of Apert's syndrome. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics, vol. 103, no. 5, p. e38-41, May 2007.

LU, X. *et al*. Association of Regional Cranial Base Deformity and Ultimate Structure in Crouzon Syndrome. Plastic and Reconstructive Surgery, vol. 143, no. 6, p. 1233e–1243e, 2019a.

LU, X. *et al*. Mandibular Spatial Reorientation and Morphological Alteration of Crouzon and Apert Syndrome. Annals of Plastic Surgery, vol. 83, no. 5, p. 568–582, 2019b.

MASPERO, C. *et al*. Nonsurgical treatment of Crouzon syndrome. Stomatologija, vol. 16, no. 2, p. 72–80, 2014.

PAWLICKI, R. *et al*. Crouzon's syndrome: tooth morphological and microanalytical evaluation. European Archives of Pediatric Dentistry: Official Journal of the European Academy of Pediatric Dentistry, v. 9, no. 4, p. 232–235, Dec. 2008.

RAPOSO-AMARAL, CE *et al*. Apert Syndrome Management: Changing Treatment Algorithm. The Journal of Craniofacial Surgery, vol. 31, no. 3, p. 648–652, jun. 2020.

REITSMA, JH *et al*. A longitudinal study of dental arch morphology in children with the syndrome of Crouzon or Apert. European Journal of Oral Sciences, vol. 121, no. 4, p. 319–327, Aug. 2013a.

REITSMA, JH *et al*. Craniofacial Stability in Patients With Crouzon or Apert Syndrome After Le Fort III Distraction Osteogenesis. The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association, vol. 50, no. 5, p. 561–569, Sept. 2013b.

REITSMA, JH *et al*. Patterns of tooth agenesis in patients with Crouzon or apert syndrome. The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association, vol. 51, no. 2, p. 178–183, mar. 2014a.

REITSMA, JH *et al*. Dental maturation in children with the syndrome of crouton and aperture. The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association, vol. 51, no. 6, p. 639–644, nov. 2014b.

STAVROPOULOS, D. *et al*. Dental agenesis patterns in Crouzon syndrome. Swedish Dental Journal, vol. 35, no. 4, p. 195–201, 2011.

TONG, H. *et al*. Midface Distraction Osteogenesis Using a Modified External Device With Elastic Distraction for Crouzon Syndrome. The Journal of Craniofacial Surgery, vol. 28, no. 6, p. 1573–1577, Sept. 2017.

TORUN, GS; AKBULUT, A. Crouzon syndrome with multiple supernumerary teeth. Nigerian Journal of Clinical Practice, vol. 20, no. 2, p. 261–263, Feb. 2017.

CHAPTER V

SYNDROMES OF DENTAL INTEREST: RETT SYNDROME

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ABSTRACT

RETT syndrome is a severe and progressive neurological development disorder with broad neurological and behavioral manifestations, its incidence is 1:10000-15000 and it is the second leading cause of severe intellectual disability in women. It is divided into four phases, stagnation from 6 to 18 months, rapid regression from the first to the fourth year, pseudo stationary from two to 10, and late psychomotor deterioration at 10 years or more. The oral changes reported in these patients can result from two main causes, side effects of drugs and the syndrome itself. Side effects are predominantly caused by anxiolytics and anticonvulsants, among the effects are xerostomia, glossitis, erythema multiforme, gingival hyperplasia, dysphagia, and tongue paralysis. The changes resulting from the syndrome itself are bruxism, anterior open bite, high palate, and sucking habits. Dental care can be aided by behavioral techniques, which are very useful in cases where there is an autistic complex, and also by props that help maintain stability and mouth opening during exploration and intervention. Hygiene instructions for caregivers and periodic consultations are important to prevent gingivitis and periodontitis. During care, it is also important to check whether there is non-physiological wear due to bruxism. In-depth knowledge of the syndrome is important for adequate treatment, given that changes in other systems affect oral health.

Keywords: RETT Syndrome, Bruxism, Hygiene instruction, Side Effects.

1 INTRODUCTION

RETT syndrome (RTT) is a severe and progressive neurodevelopmental disorder with broad neurological and behavioral manifestations (Banerjee *et al*., 2019)**.**It was first described by Andreas Rett in 1996 (Bianco; Rota, 2018), its incidence is 1:10,000-15,000 and is the second leading cause of severe intellectual disability in women(BANERJEE *et al*., 2019)**.**

This syndrome mainly affects women and occurs due to a change linked to the X chromosome (Bianco; Rota, 2018) the vast majority of cases are paternal, which justifies the higher incidence in women, rare cases of affected men present high rates of encephalopathy and have a shorter lifespan (Crosson *et al*., 2017)

RTT can be classified as classic or atypical/variant, which are the variant with preserved speech, the early epileptic manifestation variant and the congenital variant (Mezzedimi *et al*., 2017). It results in more than 90% of cases of mutations in the MECP2 gene (Banerjee *et al*., 2019)**,**other genes may also be involved, especially in variants of the

syndrome, such as CDKL5, in the early seizure variant, and FOXG1, in the congenital variant (Bianco; Rota, 2018; Mezzedimi *et al*., 2017).

2. CLINICAL FEATURES

RTT is characterized by an apparently normal prenatal and perinatal period, with stagnation of neurodevelopment between the ages of six andeighteen months of life, leaving shortly afterwards forloss of speech ability and sudden deterioration of cognitive abilities and intentional manual skills (Crosson *et al*., 2017), and finally a framework of stabilization and partial recovery (Feldman; Banerjee; Sur, 2016; Bianco; Rota, 2018). Based on this pattern, RTT is divided into four phases, stagnation from 6 to 18 months, rapid regression from the first to the fourth year, pseudostationary from 2 to 10 and late psychomotor deterioration at 10 years or more (Müller, 2019).

In conditions with more pronounced regression of cognitive abilities, the manifestation of autistic behavior, apraxia and tremor is common. Epileptic conditions, hyperventilation, periods of apnea upon awakening, progressive muscular atrophy of the extremities of the hands and legs, weight loss, growth retardation, kyphosis can also be found in these patients (Bianco; Rota, 2018) and scoliosis, which can interfere with posture and mobility as well as the functioning of the digestive and respiratory system (Mackay *et al*., 2018).

The oral changes reported in these patients can result from two main causes, side effects of drugs and the syndrome itself. Side effects are predominantly caused by anxiolytics and anticonvulsants, among the effects are xerostomia, glossitis, erythema multiforme, gingival hyperplasia, dysphagia and tongue paralysis. The changes resulting from the syndrome itself are bruxism, anterior open bite, high palate and sucking habits (Bianco; Rota, 2018). The oromotor weakness present in these cases reduces the ability to chew and swallow, which increases the risk of aspiration (Mackay *et al*., 2018), this difficulty in swallowing often causes an increase in saliva production and consequent excessive drooling, which impacts children's quality of life (Bernardo *et al*., 2019).

With adequate attention to orthopedic complications, seizure control, and nutrition, women with RTT can survive into middle age or beyond (Kyle; Vashi; Justice, 2018), but in some cases unexpected death occurs, the most common causes of death. sudden onset are those that occur during epileptic seizure, respiratory failure, aspiration, acute gastric perforation and cardiac arrhythmia (Crosson *et al*., 2017).

3. DIAGNOSIS

The diagnosis is made based on a series of criteria that are divided into main criteria, exclusion criteria and supporting criteria. To be diagnosed as classic RTT, a period of regression followed by recovery or stabilization, all the main criteria and exclusion, and no supporting criteria are necessary, to be diagnosed as atypical/variant RTT, a period of regression followed by recovery or stabilization and at least 2 of the main criteria and five of the eleven supporting criteria (Neul *et al*., 2010).

Legend. List of criteria used in the diagnosis.

Main Criteria	Exclusion Criteria for Classic RTT	Support Criteria for Atypical RTT
• Partial or complete loss of acquired manual skills. • Partial or total loss of acquired spoken language • Gait abnormalities: impaired (dyspraxic) or lack of ability. • Stereotypical hand movements such as wringing/shaking hands, clapping/slapping, mouthing, and washing/scrubbing	• Brain injury secondary to trauma (peri- or postnatal), neurometabolic disease, or severe infection causing neurological problems • Grossly abnormal psychomotor development in the first 6 months of life	• Breathing disorders when awake • Daytime bruxism • Impaired sleep pattern • Abnormal muscle tone • Peripheral vasomotor disorders • Scoliosis/kyphosis • Growth retardation • Small, cold hands and feet • Inappropriate sounds when laughing/screaming • Decreased response to pain • Intense visual communication - "pointing eyes"

4. DENTAL TREATMENT

There is no specific treatment protocol, so it is focused on the signs and symptoms presented by patients, with great importance for prevention. Dental care for patients with RTT can be aided by behavioral techniques, which are very useful in cases where there is an autistic complex, and also by props that help maintain stability and mouth opening during exploration and intervention. In more complex cases and procedures with greater risk, the

use of nitrous oxide combined or not with midazolam or even general anesthesia can be used (Bianco; Rota, 2018).

Parafunctional habits and periodontal problems are more common than cavities in these cases. The accumulation of plaque resulting from the difficulty in cleaning patients by caregivers is the main responsible for cases of gingivitis and periodontitis, which is why it is important to educate patients and caregivers, thus preventing not only cases of gingivitis and periodontitis, but also cavities and other related diseases. Manual brushes are the most recommended for cleaning as the noise from electric brushes can be uncomfortable for patients. Even though cavities are less common, preventive treatment is important, assistance from caregivers, topical application of fluoride and frequent visits to the dentist are important parts of this approach (Mezzedimi *et al*., 2017).

Bruxism, especially during the day, is frequently described among oral changes, but it tends to regress with age. Monitoring is important to assess the wear of dental elements and thus determine whether or not intervention is necessary. As gastroesophageal reflux is often present in these patients, extra attention is needed as wear and tear can be intensified (Lai *et al*., 2018).

Treatment with injection of botulinum toxin A into the salivary glands of patients with neurodegenerative disorders is efficient in reducing saliva production and consequently reducing excessive drooling. This procedure can be carried out under ultrasound guidance to increase the chances of success. Eating and bruxism also improve with treatment, but all these benefits are temporary, lasting only a few weeks (Bernardo *et al*., 2019).

5. DISCUSSION

During dental care for patients with RTT it is necessary to take a series of precautions, the regression of cognitive abilities results in changes in behavior and weakness or motor, it is often necessary to use a conditioning technique and there is difficulty in exploring and intervening in the oral cavity (Bianco; Rota, 2018), in addition to increasing the risk of aspiration (Mackay *et al*., 2018).

Behavioral changes also make oral hygiene difficult for family members and caregivers, leading to gingivitis and periodontitis constantly present in these patients. Regular consultations for prophylactic treatment are important for the control and prevention of these changes (Mezzedimi *et al*., 2017), during these consultations it is also important to assess the level of wear on dental elements, as bruxism is common, and thus define whether intervention is necessary *(Lai et al*., 2018). There is no definition in the literature of a specific

dental protocol to approach these patients, so each case must be approached individually, as in any case of a special patient with a neurological disorder, as it is necessary to understand whether the patient has any capacity for cooperation, accepting assistance from caregivers and even understanding dental treatment.

Treatment with injection of Botulinum Toxin A into the salivary glands can be done to slightly improve patients' quality of life, reducing the volume of saliva and improving bruxism and eating for a certain period of time (Bernardo *et al*., 2019). The use of protective plates for bruxism is controversial, mainly due to sucking habits, breathing difficulties and poor oral hygiene. Some authors use a soft resin plate in the occlusal contact area. Additive therapy with light-cured resins to compensate for dental wear appears to be a good alternative in cases of excessive wear, thus avoiding dentin sensitivity and pulpitis (Fuertez-Golzalez; Silvestre; Almerich-Silla, 2011).

6. CONCLUSION

The neurodevelopmental disorder in RTT is responsible for a major challenge to be faced by the dental surgeon during care. Changing behavior requires mastery of conditioning, sedation and general anesthesia techniques. The difficulty in cleaning requires creative and persistent approaches, with periodic control carried out in preventive consultations and control of the treatments carried out. Changes in other systems influence oral health in other ways, such as reflux and adverse effects of medications, so that recognizing the disease, its stages, and deepening knowledge of the syndrome is important for the healthcare team to promote a better quality of life for people with RTT syndrome.

REFERENCES

BANERJEE, A. *et al*. Towards a better diagnosis and treatment of Rett syndrome: a model synaptic disorder. Brain: A Journal of Neurology, vol. 142, no. 2, p. 239–248, 01 2019.

BERNARDO, P. *et al*. The Treatment of Hypersalivation in Rett Syndrome with Botulinum Toxin: Efficacy and Clinical Implications. Neurology and Therapy, vol. 8, no. 1, p. 155–160, jun. 2019.

BIANCO, E.; ROTA, D. Oral findings in Rett syndrome: An update and review of the literature. Dental and Medical Problems, vol. 55, no. 4, p. 441–445, Dec. 2018.

CHATTOPADHYAY, S.; ARORA, R. The ironies of human mind: a case of Rett syndrome. Ethiopian Journal of Health Sciences, vol. 24, no. 2, p. 171–174, apr. 2014.

CROSSON, J. *et al.* Evaluation of QTc in Rett syndrome: Correlation with age, severity, and genotype. American Journal of Medical Genetics. Part A, vol. 173, no. 6, p. 1495–1501, jun. 2017.

FELDMAN, D.; BANERJEE, A.; SUR, M. Developmental Dynamics of Rett Syndrome. Neural Plasticity, vol. 2016, p. 6154080, 2016.

LAI, YYL *et al*. Oral health experiences of individuals with Rett syndrome: a retrospective study. BMC oral health, vol. 18, no. 1, p. 195, 29 2018.

MACKAY, J. *et al*. Respiratory morbidity in Rett syndrome: an observational study. Developmental Medicine and Child Neurology, vol. 60, n. 9, p. 951–957, 2018.

MEZZEDIMI, C. *et al*. Dysphagia in Rett Syndrome: A Descriptive Study. The Annals of Otology, Rhinology, and Laryngology, vol. 126, no. 9, p. 640–645, Sept. 2017.

MÜLLER, M. Disturbed redox homeostasis and oxidative stress: Potential players in the developmental regression in Rett syndrome. Neuroscience and Biobehavioral Reviews, vol. 98, p. 154–163, 2019.

NEUL, JL *et al*. Rett Syndrome: Revised Diagnostic Criteria and Nomenclature. Annals of neurology, vol. 68, no. 6, p. 944–950, Dec. 2010.

CHAPTER VI

SYNDROMES OF DENTAL INTEREST: NOONAN'S SYNDROME

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ABSTRACT

Noonan syndrome (NS) is an autosomal dominant disease affecting men and women equally and has an estimated incidence of 1:1000 to 1:2500 live births. It is genetically heterogeneous, but common clinical features of the syndrome include hypertelorism, flat ears, down-sloping eyes, webbed neck, congenital heart disease, short stature, chest deformity, and intellectual disability. Patients with NS often have pulmonary valve stenosis or other less frequent heart diseases. Both require surgical modalities that have low early mortality, despite the complexity of the procedures. Oral findings in NS include micrognathia, high-arched palate, dental malocclusion, impacted teeth, and giant cell lesions in the maxilla and mandible. Patients with NS often present with tooth decay and gum problems, therefore, an annual evaluation is recommended. The treatment of malocclusion resulting from skeletal changes is generally initiated at the beginning of mixed dentition by the orthodontist and when orthodontic treatment is not sufficient, orthognathic surgery can be performed. The procedures to be performed must take into account the hematological and morphological changes that make the anesthetic management and intubation of patients difficult in cases that require general anesthesia.

Keywords: Nonnan's Syndrome, Maxillofacial alterations, Orthognathic surgery, Malocclusion.

1. INTRODUCTION

Noonan syndrome (NS) is an autosomal dominant disease, first reported by Noonan and Ehmke, affects men and women equally and has an estimated incidence of 1:1000 to 1:2500 live births (Asahi *et al*., 2015).

She is genetically heterogeneous and shows considerable clinical overlap with other sopathies, a specific class of disorders caused by germline mutations of proteins encoding genes of the RAS/MAPK pathway that represents a pathway of activation of genes and proteins that function in differentiation, growth, and cell cycle senescence. Approximately half of the known mutations are in the protein tyrosine phosphatase receptor, PTPN 11 gene (Bhambhani; Muenke, 2014; Croonen *et al*., 2017).

More than 80% of patients with NS have cardiac involvement, making it the second genetic syndrome most associated with congenital heart disease (Kawakami *et al*., 2016)

2. CHARACTERISTICS OF THE SYNDROME

Craniofacial features of NS include relative macrocephaly, distinct "triangular facies" with a high forehead, hypertelorism, pointed chin, downward-sloping palpebral fissures, epicanthic folds, ptosis, posteriorly rotated ears with thick helix(Cao *et al*., 2017; Lutz *et al*., 2020). Other features include a webbed neck, congenital heart disease, short stature, chest deformity, and intellectual disability (Asahi *et al*., 2015), in addition to other less common problems such as digestive problems, swallowing difficulties, cryptorchidism, lymphedema, joint or muscle pain, coagulation deficiencies, fingers with blunt ends, and keloids (Emral; Akcam, 2009).

Some non-specific prenatal anomalies are common among patients with NS, such as increased nuchal translucency, polyhydramnios, and abnormal maternal triple serum screening, the most common fetal morphological anomaly is hydrothorax (Bhambhani; Muenke, 2014).

Birth weight and length are usually normal or slightly subnormal. In the first year of life, there is a rapid decline in length gain. The mechanism of stunted growth has been variously reported to be intrinsic or a consequence of dysregulation of RAS/MAPK signaling itself, insufficient growth hormone secretion and growth hormone resistance (Croonen *et al*., 2018).

Most babies with NS have feeding difficulties with poor sucking, prolonged feeding time, and gastroesophageal reflux, so some need to be fed through a tube for 2 weeks or more. These problems are most often resolved by 15 months of age (Roberts *et al*., 2013).

Patients with NS often have pulmonary valve stenosis, but may also have other heart diseases such as hypertrophic obstructive cardiomyopathy, atrial septal defect, inter-ventricular septal defect, and patent ductus arteriosus (Asahi *et al*., 2015). Finally, there is an increased risk of developing solid tumors such as multiple giant cell lesions, embryonal rhabdomyosarcoma, neuroblastoma, genital and skin tumors, and blood cancers (Morice *et al*., 2018).

3. DENTAL FEATURES

Oral findings include micrognathia, high-arched palate, dental malocclusion, impacted teeth, and giant cell lesions in the maxilla and mandible (Cao *et al*., 2017). The incidence of open bite and posterior crossbite is higher than in the general population (Lutz *et al*., 2020), which suggests that it is due to the early closure of the cranial sutures, which

influences the growth of the dental arch and results in a lack of growth of the palatal suture and consequently alters the shape of the palate (Kawakami *et al*., 2016). Some individuals with NS develop mandibular cysts characterized by multinucleated giant cells within a fibrous stroma that is indistinguishable from cherubism (Romano *et al*., 2010).

4. DIAGNOSIS

The diagnosis of NS depends mainly on the identification of clinical characteristics (Bhambhani; Muenke, 2014). It should be considered in all fetuses with a normal karyotype and increased nuchal translucency, especially when cardiac anomalies, polyhydramnios, and/or multiple strokes are observed (Bhambhani; Muenke, 2014).

There is a scoring system that helps diagnose patients with the disease. Until recently, the diagnosis was made based on clinical features alone, but molecular genetic testing can confirm 70% of cases (Bhambhani; Muenke, 2014).

Most cases are sporadic. In familial cases, autosomal dominant inheritance is confirmed. The risk of developing NS in an affected person's sibling is 50% if the parent is affected, but is less than 1% if the parent is unaffected. Preimplantation genetic diagnosis may be offered in familial cases with known mutations (Bhambhani; Muenke, 2014)

5. TREATMENT

Many people with NS report problems related to pain, decreased muscle strength, fatigue and "clumsiness", generally causing difficulties in daily life. Physical assessments and guidance and/or occupational therapy should be considered to increase participation in daily life (Croonen *et al*., 2017). Patients with NS frequently present with multiple cardiac lesions that need to be repaired with a wide spectrum of operations, with early mortality being low despite the complexity of the procedure (Hemmati *et al*., 2019). Patients with NS may have a combination of platelet abnormalities and coagulation factor defects, however, no strong correlation can be established between coagulation abnormalities and the risk of excessive perioperative bleeding (Lutz *et al*., 2020). Furthermore, several studies have reported difficult intubation due to limited mouth opening, webbed neck with cervical spine anomalies, and other craniofacial anomalies (Asahi *et al*., 2015).

6. DENTAL TREATMENT

Patients with NS often present with tooth decay and gum problems, therefore, it is recommended to carry out an annual assessment, starting between 1 and 2 years, to

carry out oral prophylaxis, use of sealants, and carry out preventive resin restorations, early treatment of dental anomalies, such as extraction of decayed, supernumerary and submerged teeth, and monitoring of dental crowding and malocclusion. Treatment of malocclusion is generally started at the beginning of mixed dentition by the orthodontist. Rehabilitation of the muscles of the lower third of the face, often impaired in patients with NS, is also essential (Lutz *et al*., 2020).

The orthognathic surgery may be indicated due to specific facial characteristics such as a high arched palate with open bite, reduced sagittal and transverse maxillary and mandibular dimensions, and increased facial height that becomes more evident with age (Morice *et al*., 2018). In these cases, referral to a hematologist is recommended for a complete blood test, and even in the case of normal results, the hematologist must establish specific guidelines for perioperative management (Lutz *et al*., 2020).

Anesthetic management of these patients is challenging due to congenital heart disease, hemostatic disorders, and airway anomalies. Patients with NS may have a combination of platelet abnormalities and coagulation factor defects, however, no strong correlation can be established between coagulation abnormalities and the risk of excessive perioperative bleeding (Lutz *et al*., 2020). Furthermore, several studies have reported difficult intubation due to limited mouth opening, webbed neck with cervical spine anomalies, and other craniofacial anomalies (Asahi *et al*., 2015).

7. DISCUSSION

The main characteristics of NS are hypertelorism, low ears, downward-slanting eyes, webbed neck, congenital heart disease, short stature, chest deformity, and intellectual disability. Patients with NS often have pulmonary valve stenosis or other less common heart conditions (Asahi *et al*., 2015), which are repaired with a wide spectrum of operations that present low early mortality, despite the complexity of the procedure (Hemmati *et al*., 2019). Many patients with NS report problems related to pain, decreased muscle strength, fatigue, and clumsiness, and physical evaluations and guidance and/or occupational therapy are therefore recommended (Croonen *et al*., 2017).

Oral findings in NS include micrognathia, high-arched palate, dental malocclusion, impacted teeth, and giant cell lesions in the maxilla and mandible (Cao *et al*., 2017). Regarding conduct during routine consultations, an annual assessment is recommended from the age of 1 or 2 to carry out oral prophylaxis, early treatment of dental anomalies, and monitoring of dental crowding and malocclusion (Lutz *et al*., 2020). The treatment of

malocclusion resulting from skeletal changes is generally started at the beginning of mixed dentition by the orthodontist and when orthodontic treatment is not sufficient, orthognathic surgery can be performed. In these cases, it is important to consult a hematologist to perform a complete blood test and establish specific perioperative management guidelines. During procedures, anesthetic management and intubation are made difficult by systemic changes present in patients (Asahi *et al*., 2015; Lutz *et al*., 2020).

8. CONCLUSION

Due to oral changes and the oral health profile of patients with NS, monitoring by a dental surgeon is necessary from the first years of life. The procedures to be performed must take into account the hematological and morphological changes that make anesthetic management and intubation of patients difficult in cases requiring general anesthesia.

REFERENCES

ASAHI, Y. *et al*. Repeated General Anesthesia in a Patient With Noonan Syndrome. Anesthesia Progress, v. 62, no. 2, p. 71–73, 2015.

BHAMBHANI, V.; MUENKE, M. Noonan syndrome. American Family Physician, vol. 89, no. 1, p. 37–43, 1 Jan. 2014.

CAO, H. *et al*. A review of craniofacial and dental findings of the RASopathies. Orthodontics & Craniofacial Research, vol. 20 Suppl 1, p. 32–38, jun. 2017.

CARDIEL RÍOS, SA Correction of a severe Class II malocclusion in a patient with Noonan syndrome. American Journal of Orthodontics and Dentofacial Orthopedics: Official Publication of the American Association of Orthodontists, Its Constituent Societies, and the American Board of Orthodontics, vol. 150, n. 3, p. 511–520, Sept. 2016.

CROONEN, EA *et al*. Motor performance in children with Noonan syndrome. American Journal of Medical Genetics. Part A, vol. 173, no. 9, p. 2335–2345, Sept. 2017.

CROONEN, EA *et al*. First-year growth in children with Noonan syndrome: Associated with feeding problems? American Journal of Medical Genetics. Part A, vol. 176, no. 4, p. 951–958, apr. 2018.

EMRAL, ME; AKCAM, MO Noonan syndrome: a case report. Journal of Oral Science, vol. 51, no. 2, p. 301–306, jun. 2009.

HEMMATI, P. *et al*. Early Outcomes of Cardiac Surgery in Patients with Noonan Syndrome. Seminars in Thoracic and Cardiovascular Surgery, vol. 31, no. 3, p. 507–513, 2019.

KAWAKAMI, M. *et al*. Surgical Orthodontic Treatment for Open Bite in Noonan Syndrome Patient: A Case Report. The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association, vol. 53, no. 2, p. 253–258, 2016.

LUTZ, J.-C. *et al*. Dental and maxillofacial characteristics of Noonan Syndrome: Case series of ten patients. Journal of Cranio-Maxillo-Facial Surgery: Official Publication of the European Association for Cranio-Maxillo-Facial Surgery, v. 48, n. 3, p. 242–250, mar. 2020.

MORICE, A. *et al*. Preoperative Detailed Coagulation Tests Are Required in Patients With Noonan Syndrome. Journal of Oral and Maxillofacial Surgery: Official Journal of the American Association of Oral and Maxillofacial Surgeons, vol. 76, no. 7, p. 1553–1558, Jul. 2018.

ROBERTS, AE *et al*. Noonan syndrome. Lancet (London, England), v. 381, no. 9863, p. 333–342, 26 Jan. 2013.

ROMANO, AA *et al*. Noonan syndrome: clinical features, diagnosis, and management guidelines. Pediatrics, vol. 126, no. 4, p. 746–759, Oct. 2010.

CHAPTER VII

SYNDROMES OF DENTAL INTEREST: TOURETTE SYNDROME

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ABSTRACT

Gilles de la Tourette syndrome, or just Tourette syndrome (TS), is a condition that affects neurodevelopment and its onset in childhood. It is characterized by motor and vocal tics and associated psychiatric comorbidities, such as OCD, and ADHD, in addition to phobias and anxiety disorders. Dental manifestations are presented mainly as self-mutations. Clinical findings make the diagnosis and the treatment of TS is individualized and must be carried out by a multidisciplinary team.

Keywords: Tourette syndrome, Dentistry, dental treatment.

1. INTRODUCTION

Gilles de la Tourette syndrome, or just Tourette syndrome (TS), is a condition that affects neurodevelopment and begins in childhood. It was first described in 1885 by the French doctor Georges Gilles de la Tourette (Tourette, 1885). It can be defined as motor and vocal tics, which may or may not occur concomitantly and present as sudden, recurrent, rapid and non-rhythmic movements and sounds, generally exacerbated by anxiety or stress (Zinner & Coffey, 2009; Cavanna *et al*., 2009; Bloch *et al*., 2011; Mcnaught & Mink, 2011).

TS can be consider multicausal and the definitive etiological factors are still unknown. However, the condition may be associated with neuroanatomical and neurophysiological changes, such as a disorder in the mesolimbic pathway, one of the brain's dopaminergic pathways, which leads to a disinhibition of the motor and limbic system (Jankovic, 2001), in addition to environmental factors, such as pre-and postnatal stress, streptococcal infection (Hoekstra *et al*., 2013; Mathews *et al*., 2014) and genetic factors, being considered an autosomal dominant disorder, as detected in studies with twins and relatives (Jankovic, 2001; Pauls *et al*., 2014).

It is estimated that it occurs between 0.3% and 0.8% of the world's child population, with a higher prevalence in males, around 4 to 1. Symptoms normally persist for more than a year and manifest themselves before the child is 18 years old. individual, more precisely between the ages of 5 and 7 years. With a tendency to decrease with increasing age, 2/3 of individuals experience remission of symptoms until early adulthood (Freeman *et al*., 2000; Robertson, 2015; Scharf *et al*., 2015).

2. CLINICAL MANIFESTATIONS AND DIAGNOSIS

The main clinical manifestations of TS are motor and vocal tics, which appear before the age of 18 and become strongly established around the age of 12, the motor ones a few years before the vocal ones, initially in the face region spreading to the neck, shoulders and extremities as the condition worsens. They are evident for 1 year or more, manifesting several times a day, and can be as simple as blinking, movements of the jaw and neck, sniffling, coughing, nose wrenching, to more complex ones such as uttering words or phrases, squatting, jumping and excessive touching. They can also be considered temporary tics if one or more motor and/or vocal tics manifest for less than 12 months, if before the individual's 18th birthday, the tics exceed the 12 months they are established as persistent tics (Apa, 2013; Scharf *et al*., 2015; Gloor *et al*., 2016)

Anxiety and stress aggravate tics, which often appear to release this tension. Furthermore, patients with TS may present some comorbidities, mainly obsessive-compulsive disorder – OCD in 50% of patients and Attention Deficit Hyperactivity Disorder – ADHD in 54% (Banaschewski *et al*., 2003; Hirschtritt *et al*., 2015; Efron & Dale, 2018). Other comorbidities also observed are sleep disorders, learning disorders, social cognition, self-harm, anxiety and depression, with 5 to 15% of patients still having autism spectrum disorder - ASD (Darrow *et al*., 2017).

The main oral manifestations present in patients with TS are the motor tics themselves in the region, such as the act of constantly licking the lips and nibbling the lips, tongue and buccal mucosa, which causes pain and injuries, in addition to coughing, jaw clicking, bruxism, tooth fractures and touching the gingival tissue with the nails (Friedlander & Cummings, 1992; Shimoyama *et al*., 2003; Hansen *et al*., 2015). In this aspect, self-mutilation in the oral region becomes a manifestation of great clinical importance, given the damage it can cause to the patient, such as severe recurrent infections and difficulty eating and speaking. Constant touching of the gingival tissue with the nails, for example, can lead to the extraction of permanent teeth (Vogel, 1998, Leksell & Edvardson, 2005; Lee *et al*., 2016).

The diagnosis of TSIt is based on the observation of clinical findings, more precisely the motor and vocal tics and the behavioral disorders present, such as anxiety, OCD, and ADHD, and the patient's history, time of appearance of the tics, and daily frequency. Likewise, the dental diagnosis is made based on clinical findings, the presence of pain, lesions, and tics in the oral region, in addition to the patient's history. The differential diagnosis occurs among other conditions that may be accompanied by abnormal movements, including Hun-

tington's Disease, Wilson's Disease, multiple sclerosis, head trauma, and stroke (Tourette, 1885; Teixeira *et al*., 2011; APA, 2013).

3. TREATMENT

TS has no cure and its treatment encompasses a combination of behavioral, educational and pharmacological techniques on an individual basis, according to the severity of the tics and the existence of comorbidities that depend on specific treatment, and must be carried out by a multidisciplinary team. Mild cases of TS, for example, can be controlled with counseling and monitoring, in which patients are taught to reorganize or suppress the need to perform tics and, above all, maintain their self-confidence and self-esteem. The most severe cases in which the individual is unable to function in society or suffers isolation or stigmatization must be treated with medication (Shapiro *et al*., 1987; Hallett, 2015; Gloor *et al*., 2016; Efron & Dale, 2018).

The most common medications for treating TS involve alpha-2-adrenergic agonists antidopaminergic, anticonvulsants and benzodiazepines, which act directly to control tics and anxiety. For ADHD, the drug treatment of choice may be based on stimulants such as methylphenidate and dextroamphetamine and alternatively with norepinephrine reuptake inhibitors such as Atomoxetine and OCD can be treated with selective serotonin reuptake inhibitors (Hartmann & Worbe, 2013; Hansen *et al*., 2015; Hallett, 2015; Gloor *et al*., 2016; Efron & Dale, 2018).

Botulinum toxin has been used as an alternative treatment in mild cases of TS. Intramuscular injections, aim to reduce tics and pain, mainly in the neck, shoulder, and eyes, and severe vocal tics can also be treated through injections into the larynx. However, the benefits of botulinum toxin are temporary, with the effects remaining for 3 to 6 months (Kwak *et al*., 2000; Simpson, *et al*., 2008; Termine *et al*., 2013; Kurlan, 2014; Moretti, 2020).

An alternative in the treatment of TS is the use of Cannabis sativa L. or marijuana, specifically its most psychoactive ingredient, Tetrahydrocannabinol- THC, which affects the activity of excitatory and inhibitory neurotransmitters and monoamines such as dopamine and noradrenaline, alleviating the frequency of tics (Pertwee, 2008; Müller-Vahl, 2013a).

Also to control tics, in cases extremes in which medication is not effective and patients are considered resistant to treatment, deep brain stimulation surgery can be used, which consists of a surgical procedure of placing stimulating electrodes in specific regions of the brain, connected to a neurostimulator to perform of neuromodulation (Savica *et al*., 2012; Müller-Vahl, 2013b; Baldermann *et al*., 2015).

4. DENTAL TREATMENT

Dental treatment for TS must be individualized given the systemic conditions, use of medications, and specific dental manifestations in each patient, with pediatric dentistry being an important area of dentistry in these cases, due to the first manifestations of this condition occurring in childhood. Oral health education and hygiene instructions such as proper use of toothbrush and floss are essential for a good treatment prognosis. Consultations should be limited in time and the patient's pace should be considered when carrying out the procedures, with family collaboration being very important throughout the treatment (Friedlander & Cummings, 1992; Hansen *et al*., 2015; Lee *et al*., 2016).

The stress of dental treatment can exacerbate tics and make the patient even more anxious, hindering the smooth progress of care. Therefore, behavioral management techniques are recommended, such as "tell-show-do", voice control, positive reinforcement, and distraction, among others. Contact between the dentist and the responsible doctor is essential for controlling and prescribing medication, checking drug interactions, and deciding whether to use local or general anesthetics (Friedlander & Cummings, 1992; Kurlan, 2014; Hansen *et al*., 2015).

The treatment of patients with orofacial pain, bruxism, temporomandibular disorders, and dental fractures resulting from these conditions must follow normal protocols, such as the use of plates, corresponding medication, and necessary restorations, in addition to the use of botulinum toxin in specific cases, always analyzing the individual condition. of each patient (Friedlander & Cummings, 1992; Hansen *et al*., 2015; Moretti, 2020).

For the treatment of self-mutilation injuries, it is recommended, in addition to behavioral and pharmacological control, the use of polyvinyl or acrylic plates as a conservative treatment and in serious cases in which there is severe mutilation and the patient has no discernment of their actions or this is reduced due to Due to the severity of their mental conditions, temporary intermaxillary fixation until tooth extractions can be considered (Friedlander & Cummings, 1992; Shimoyama *et al*., 2003; Leksell & Edvardson, 2005; Hansen *et al*., 2015; Lee *et al*., 2016).

5. DISCUSSION

An early diagnosis should be sought based on the patient's conditions, avoiding unnecessary physical and psychological suffering for the patient and his family. Care for patients with TS is strengthened by cooperation between dentists and other health profes-

sionals, through a multidisciplinary team. The assistance of a neurologist or psychiatrist is important, mainly due to the anxiety that the treatment itself can cause, both systemic and dental, to avoid further harming the patient and increasing their stress levels (Friedlander & Cummings, 1992; Leksell & Edvardson, 2005).

The first medical contact of patients with signs of self-mutilation in the oral region is normally with the dentist, and he must be prepared to assist in the diagnosis and carry out the necessary medical referrals, considering that these injuries have a strong relationship with psychiatric comorbidities and of behavior, which appear associated with TS (Leksell & Edvardson, 2005; Lee *et al*., 2016).

Regarding pharmacological treatment, it is important to highlight that patients who use haloperidol may experience cardiac effects that influence dental treatment, such as tachycardia, postural hypotension, and uncontrolled blood pressure. Therefore, it is advisable to request a complete blood count, with a platelet count (Friedlander & Cummings, 1992; Loureiro *et al*., 2005; Hansen *et al*., 2015).

6. CONCLUSION

Knowing the general aspects of this syndrome is essential for health professionals, considering that early diagnosis and treatment are essential for the patient's good prognosis. In addition to systemic conditions, the oral health of patients with TS must receive adequate attention, aiming for quality of life and dignity, control of pain and the consequences of self-mutilation. There must be constant cooperation between the patient, family, caregivers and the multidisciplinary healthcare team.

REFERENCES

APA. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th edn. Arlington, VA: American Psychiatric Publishing; 2013.

BALDERMANN, JC; SCHÜLLER, T.; HUYS, D.; BECKER, I.; TIMMERMANN, L.; JESSEN, F.; VISSER-VANDEWALLE, V.; KUHN, J. Deep Brain Stimulation for Tourette-Syndrome: A Systematic Review and Meta-Analysis. Brain Stimulation. 2016;9(2):296-304. doi: 10.1016/j.brs.2015.11.005.

BANASCHEWSKI, T.; WOERNER, W.; ROTHENBERGER, A. Premonitory sensory phenomena and suppressibility of tics in Tourette syndrome: developmental aspects in children and adolescents. Dev Med Child Neurol. 2003;45:700–3.

BLOCH, M.; STATE, M.; PITTENGER, C. Recent advances in Tourette syndrome. Curr Opin Neurol. 2011;24:119-25.

CAVANNA, AE; SERVO, S.; MONACO F.; ROBERTSON, MM The behavioral spectrum of Gilles de la Tourette syndrome. J Neuropsychiatry Clin Neurosci. 2009;21:13-23.

DARROW, SM; GRADOS, M.; SANDOR, P.; HIRSCHTRITT, ME; ILLMANN, C.; ET AL.Autism Spectrum symptoms in a Tourette's disorder sample. J. Am. Acad. Child Adolescence. Psychiatry 2017; 56:610–7.e1.

EFRON, D.; DALE, RC. Tics and Tourette syndrome. J Paediatr Child Health. 2018;54(10):1148-1153. doi:10.1111/jpc.14165.

FRIEDLANDER, AH; CUMMINGS, JL. Dental treatment of patients with Gilles de la Tourette's syndrome. Oral Surg Oral Med Oral Pathol. 1992;73: 299-303.

TOURETTE, GG Etude sur une affection nerveuse caracterisée par de l'incoordination motrice accompagnée d'écholalie et de copralalie. Arch Neurol (Paris). 1885;9:19-42;158-200.

HALLETT, M. Tourette Syndrome: Update. Brain Dev. 2015;37(7):651-655. doi:10.1016/j.braindev.2014.11.005.

HANSEN, JK; JACOBSEN, PE; SIMONSEN, JL; HOVGAARD, O.; HAUBEK, D. Tourette syndrome and procedures related to dental treatment: a systematic review. Spec Care Dentist. 2015;35(3):99-104. doi:10.1111/scd.12098.

HARTMANN, A.; WORBE, Y. Pharmacological treatment of Gilles de la Tourette syndrome. Neurosci Biobehav Rev. 2013;37(6):1157-1161. doi:10.1016/j.neubiorev.2012.10.014.

HIRSCHTRITT, ME; LEE, PC; PAULS, DL; DION, Y.; GRADOS, MA; *et al*. Tourette Syndrome Association International Consortium for Genetics. Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. JAMA Psychiatry. 2015;72(4):325-33. doi: 10.1001/jamapsychiatry.2014.2650.

SCHARF, JM; MILLER, L.L.; GAUVIN, CA; ALABISO, J.; MATHEWS, CA; BEN-SHLOMO, Y. Population prevalence of Tourette syndrome: a systematic review and meta-analysis, Mov. Disord. 2015;30(2):221-8. doi:10.1002/mds.26089.

JANKOVIC, J. Tourette's syndrome. N Engl J Med 2001;345:1184-92.

KKOTNIM, L.; MIAE, K.; INKYUNG, H.; JIHYUN, P.; YONJOO, M. Self-inflicted Tongue Ulceration in a Patient with Tourette Syndrome: A Case Report. J Korean Acad Pediatr Dent 2016;43(3):327-333.

KURLAN, RM. Treatment of Tourette syndrome. Neurotherapeutics 2014;11:161–5.

KWAK, CH; HANNA, PA; JANKOVIC, J. Botulinumtoxin in the treatment of tics. Arch Neurol. 2000;57(8):1190–3.

LEKSELL, E.; EDVARDSON, S. A case of Tourette syndrome presenting with oral self-injurious behavior. Int J Paediatr Dent. 2005;15(5):370-374. doi:10.1111/j.1365-263X.2005.00652.x.

LOUREIRO, NIV; MATHEUS-GUIMARÃES, C.; SANTOS, DO; FABRI, RGF; RODRIGUES CR; CASTRO, HC. Tourette: inside the syndrome. Rev Psiquiatr Clín. 2005;32(4):218-230.

ROBERTSON, MM. A personal 35 years perspective on Gilles de la Tourette syndrome: prevalence, phenomenology, comorbidities, and coexisting psychopathologies. Lancet Psychiatry. 2015;21:68-87, doi:10.1016/S2215-0366(14)00132-1.

MCNAUGHT, KS; MINK, JW Advances in understanding and treatment of Tourette syndrome. Nat Rev Neurol. 2011;7:667-76.

MORETTI, A. Is botulinum toxin effective and safe for motor and phonic tics in patients affected by Tourette syndrome? A Cochrane Review summary with commentary. Dev Med Child Neurol. 2020;62(3):274-276. doi:10.1111/dmcn.14472.

MÜLLER-VAHL, KR. Surgical treatment of Tourette syndrome. Neurosci Biobehav Rev. 2013a;37(6):1178-1185. doi:10.1016/j.neubiorev.2012.09.012.

MÜLLER-VAHL, KR Treatment of Tourette syndrome with cannabinoids. Behav Neurol. 2013b;27(1):119-124. doi:10.3233/BEN-120276.

PERTWEE, RG Ligands that target cannabinoid receptors in the brain: from THC to anandamide and beyond. Addict Biol. 2008;13(2):147-59.

FREEMAN, R.D.; FAST, D.K.; BURD, L.; KERBESHIAN, J.; ROBERTSON, MM; SANDOR, P. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. Dev Med Child Neurol. 2000;42(7):436-447. doi:10.1017/s0012162200000839.

SAVICA, R.; STEAD, M.; MACK, KJ; LEE, KH; KLASSEN, BT Deep brain stimulation in tourette syndrome: a description of 3 patients with excellent outcome. Mayo Clin Proc. 2012;87(1):59-62. doi:10.1016/j.mayocp.2011.08.005

SHAPIRO, AK; SHAPIRO, E.; FULOP, G. Current status: pimozide treatment of tic and Tourette disorders. Pediatrics. 1987;79:1032-9.

SHIMOYAMA, T.; HORIE, N.; KATO, T.; NASU, D.; KANEKO, T. Tourette's syndrome with rapid deterioration by self-mutilation of the upper lip. J Clin Pediatr Dent. 2003;27:177-180.

SIMPSON, DM; BLITZER, A.; BRASHEAR, A.; COMELLA, C.; DUBINSKY, R.; HALLETT, M.; et al. Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review). Neurology. 2008;70(19):1699–706.

GLOOR, FT; WALITZA, S.Tic Disorders and Tourette Syndrome: Current Concepts of Etiology and Treatment in Children and Adolescents. Neuropediatrics. 2016;47(2):84-96. doi:10.1055/s-0035-1570492.

TEIXEIRA, LLC; PANTOJA JÚNIOR, JMS; NETO, FXP; TARGINO, MN; REED, ACP; SILVA, FA La Tourette's syndrome: literature review. Int. Otorhinolaryngol Archives. 2011;15(4):492-500. doi:10.1590/S1809-48722011000400014.

TERMINE, C., SELVINI, C., ROSSI, G.; BALOTTIN, U. Emerging treatment strategies in Tourette syndrome: what's in the pipeline? Int Rev Neurobiol 2013;112:445–80.

VOGEL, LD When children put their fingers in their mouths. Should parents and dentist's care? New York State Dental Journal. 1998;64:48–53.

ZINNER, SH; COFFEY, BJ Developmental and behavioral disorders grown up: Tourette's disorder. J Dev Behav Pediatr. 2009;30:560-73.

CHAPTER VIII

SYNDROMES OF DENTAL INTEREST: VAN DER WOUDE SYNDROME

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ABSTRACT

Van der Woude Syndrome is a rare genetic syndrome with autosomal dominant inheritance, resulting from a mutation in the gene encoding interferon regulatory factor 6 (IRF6). The prevalence of Van der Woude Syndrome is one to nine cases per 100,000 people. This clinical condition is generally evidenced by cleft lip and palate (CLP) and the presence of lip pits, which may or may not be accompanied by hypodontia. CLP are congenital craniofacial anomalies that promote changes in the development and growth of the palate and the middle third of the face. In Brazil, 1 in every 650 children born alive has CLP, however the cases in which there is an association with genetic syndromes correspond to 25%, and of this statistic, only 2% are diagnosed as Van der Woude Syndrome. The syndrome is the most common syndromic form of cleft lip and palate, and an affected person has a 50% chance of transmitting the change to their children. These patients present at least one of the following characteristics: popliteal pterygium, syndactyly, genitourinary changes, ankyloblepharon, pyramidal skin fold on the hallux or oral adhesions. The treatment and rehabilitation of patients with this syndrome involves clinical and surgical interventions carried out by a multidisciplinary team composed of the specialties: Oral and Maxillofacial Surgery, Plastic Surgery, Nursing, Physiology, Physiotherapy, Speech Therapy, Genetics, Nutrition, Pediatric Dentistry, Orthodontics, Otorhinolaryngologist, Pediatrics, Palate Prosthesis, Psychology and Social Work. It is worth highlighting that interdisciplinary work is essential for maintaining satisfactory results, mitigating complications and minimizing sequelae and that the pediatrician's role is essential for adequate treatment monitoring and efficient intercommunication between all working professionals.

Keywords: Syndrome,Van Der Woude, Dentistry.

1. INTRODUCTION

The first evidence of Van der Woude Syndrome was reported in 1845 by Demarquay, through the study of the lip pit. However, it was only in 1954 that autosomal dominant inheritance was defined by Van der Woude, who identified a genetic alteration of a single gene, presenting variable expressivity and high penetrance (Van der Woude, 1954). The probability of an individual with Van der Woude Syndrome transferring the mutation to their children is 50%. According to Trevilatto & Werneck (2014), autosomal dominant inheritances have some characteristics, as shown in table 1.Van der Woude Syndrome may be accompanied by clinical signs such as hypodontia,numerary dental anomaly, characterized by the absence of a maximum of six teeth(Capelão *et al*., 2013; Queiroga *et al*., 2016).

Table 1. Characteristics of Autosomal Dominant Syndromes

1. The phenotype has the same frequency in men and women;
2. Individuals without the syndrome, even though they are children of affected parents, do not transmit the phenotype to their descendants;
3. The phenotype appears in all generations from the affected individual;
4. The affected individual can be of either sex and have a father or mother who is equally affected.

Syndromic analysis seems simplified when based on the aforementioned characteristics. However, other factors must be investigated concomitantly (Table 2), according to Trevilatto & Werneck (2014).

Table 2. Genetic cofactors.

New mutations	Unaffected parents can generate individuals with genetic alterations at the time of fertilization, due to mutations in gametogenesis.
Germinative mosaicism	It is the condition when an unaffected person has unaltered germ cells and others containing the mutation, resulting from an error in embryogenesis.
Incomplete penetrance	Genetic phenomenon that consists of individuals who do not phenotypically manifest the mutation.
Variable expressivity	Variable expressivity consists of the manifestation of a given gene mutation in different forms, that is, it can vary from very mild to severe changes in members of a single-family group.
Local heterogeneity	It occurs when different genes, that is, from different loci, determine identical or similar clinical phenotypes. Therefore, inheritance can follow a dominant or recessive pattern, depending on the locus in which the change occurred.
Late manifestations	It occurs when the manifestation of a certain genetic disease only appears in adulthood.
Phenocopy	Phenocopy is the condition in which there is a phenotype originated by environmental factors, which becomes indistinguishable from a genetic phenotype.

Source: Trevilatto & Werneck (2014).

The prevalence of Van der Woude Syndrome is one to nine cases per 100,000 people (Orphanet, 2020). It is estimated that syndromic fissures comprise 25% of the total reported clinical cases, according to data from the Human Genome and Stem Cell Research Center (Bueno *et al*, 2015), of which only approximately 2% are diagnosed and associated with Van der Woude Syndrome (Kuchler, 2010).

2. CLINICAL MANIFESTATIONS

Cleft lip and palate

Also, according to Trevilatto & Werneck (2014), Van der Woude Syndrome is one of the main syndromes related to clinical cases of Cleft Lip and Palate (CLP). According to data from the Ministry of Health, one in every 650 children born alive has CLP (Kopko, 2016). Orofacial clefts can be classified into basically four groups: pre-incisive foramen, post-incisive foramen, trans-incisive foramen, and rare facial fissures, with the incisive foramen as an anatomical reference (*Spina et al*., 1972; Silva-Filho *et al*., 1992; Tessier, 1976). Studies indicate that the incidence of this craniofacial anomaly varies according to ethnicity, due to its multifactorial characteristics. The highest incidence (0.8 to 4.0 cases per thousand live births) is observed in Indian, Asian, and American communities. In Caucasian populations, the incidence varies from 0.9 to 2.7 cases per thousand live births. Finally, in African populations, the incidence is the lowest recorded, 0.2 to 1.7 (Deshpande & Goudy, 2019).

In the figures below from Meggiolaro *et al*., 2020, it is possible to observe the classification of fissures, when compared to the anatomical standard. The pre-incisive foramen fissure causes changes in the lips unilaterally or bilaterally, which may or may not affect the alveolar process of the maxilla. When there is no involvement of the edge, the malformation is classified as incomplete and complete, when this is reached. The post-foramen fissure is located posterior to the incisive foramen, on the palatine process of the maxilla, and causes anatomical variations in the palate, thus receiving the name complete, when there is an extension from the bony palate to the soft palate, or incomplete when it is located only on the soft palate. It is worth noting that there is no congenital cleft of the hard palate alone. The transformer incisive fissure is the most extensive and affects the upper lip (unilaterally or bilaterally), the alveolar process of the maxilla, the hard palate, and the soft palate (*Spina et al*., 1972). This classification

was modified and complemented in 1992, therefore, the median cleft was included in the group of transformer incisive clefts, even though it has a lower prevalence in the

population (Silva-Filho *et al*., 1992). Finally, rare facial fissures are a set of changes with a lower prevalence in society. Its phenotype is varied, compromising bone structures and soft tissues, such as, for example, in the orbital cavity (Tessier, 1976).

Classification of orofacial clefts

The classification of orofacial clefts is necessary as they may manifest in different ways. In Brazil, Spina's classification is the most used, which divides the clefts into four categories, having as a reference point the incisive foramen. The characteristics of the main fissures described by Spina, as well as the complementation of information proposed by other authors regarding the original classification, are presented in more detail in Chart 1.

Chart 1. Spina classification and authors' complements, author/year, type of study, definition.

Spina classification	Author/year	Type of study	Definition
Pre-incisive foramen cleft	Rodrigues *et al*., 2018; Spina, 1973	Clinical study (In vivo)	Exclusively lip fissure due to the lack of fusion of the maxillary processes with the median nasal processes. It may be unilateral, bilateral or median and complete or incomplete. It is complete when small fissures occur in the vermilion mucosa and/or lip skin and complete rupture of the lip and alveolar ridge, passing through the floor of the nose and ending in the incisive foramen. This type of cleft when not involving the alveolar ridge does not present dental anomalies. The nasal tip is deflected to the non-fissured side.

Post-incisive foramen cleft	Ortiz-Posadas *et al*., 2001; Spina et al., 1972	Clinical study (In vivo)	They are the palatal clefts resulting from the lack of fusion of the palatal processes with each other and with the nasal septum. They are medium and can only affect uvula, soft palate (incomplete) or when there is involvement of the hard palate (incomplete/complete). In this type of cleft there is no aesthetic problem as in the others, but it leads to a nasal resonance of speech due to the inadequate function of the pharyngeal fleece mechanism. It is the most common fissure to be found associated with other birth defects. The mildest form of this fissure is the bifid uvula, which does not always require a therapeutic approach.
Tran-incisive foramen cleft	Spina *et al*., 1972	Clinical study (In vivo)	It is due to the non-fusion of the mesenchyme of the lateral palatal processes of the palate and nasal septum. Reaches lip, alveolar arch and all palate. It can be unilateral or bilateral and complete or incomplete (when the lip is not affected). It is the most severe form of cleft.
Rare facial cleft	Allori *et al*., 2017; Spina 1973	Clinical study (In vivo)	They involve lips, nose, eyes and jaw. There are also cases with muscle tissue (soft palate) or bone (hard palate) deficiency under the intact mucous layer, giving a false idea of normality. The most evident sign is located in the midline of the palate, which will have a much lighter coloration than the rest of the mucosa. It is often associated with the presence of a bifid uvula.

The individual will have speech hypernasality and the symptom that the baby with this type of cleft presents is the leakage of milk through the nose. When submucosal, diagnosis is only possible through a nasofibroscopy.

Anatomical Changes

Anatomical changes vary according to the clinical case. In individuals with CLP, the classification itself demonstrates diverse changes in the lip, alveolar process, maxilla, palatine bones, and soft palate (*Spina et al*., 1972). The bony palate is made up of the palatine process of the maxilla and the horizontal plate of the palatine bones. The soft palate, on the other hand, is of muscular origin, originated mainly by the muscles: tensor of the soft palate and elevator of the soft palate with the uvula muscle (Teixeira *et al*., 2008). Palatal changes alter the fixation of the muscles that are located in the median raphe, meaning there is no adequate muscle traction on the soft palate (Manzi *et al*., 2013). In addition to musculoskeletal changes, recurrent cases of middle ear otitis are common in these patients (Sheahan *et al*., 2003) by the factor of the insertion of the muscular fibers of the tensor veli palatini and the levator veli palatini, which, in one of their main functions, during swallowing contraction, regulate the pressure inside the middle ear with the external environment (Oliveira *et al*., 2013). In more severe cases, hearing loss may occur (Sheahan *et al*., 2003). Dental complications are diverse, such as: agenesis, microdontia and gyroversion (Corrêa *et al*. 2017).

Lip pitches

One of the most striking characteristics of patients with Van der Woude Syndrome is the association with lip pits, which was the first to be highlighted in the literature, in 1845 by Demarquay (Van der Woude, 1954). In the lower lip, labial pits are bilateral malformations in the vermilion resulting from the interruption of the embryonic development process of the lateral sulcus, during the fourth gestational week. They predominantly impact aesthetics and, in isolated cases, do not generate major compromises, as they are generally obliterated (Wervenka *et al*., 1967; Warbrick *et al*., 1951).

3. DIAGNOSIS

According to Queiroga *et al*., 2016, the diagnosis can be made in clinical practice through the typical signs of the syndrome, which are: cleft lip and palate, lip pit, and high prevalence of hypodontia. Another point to be emphasized is the importance of differential diagnosis, since other syndromes may have signs of Van der Woude Syndrome (Sanchis-Calvo *et al*., 2006).

Finally, as in the study of Meggiolaro *et al*., 2020, genetic mapping and counseling are the best means of finalizing the diagnosis in cases of this syndrome.

4. TREATMENT

The treatment and rehabilitation of CLP, both isolated and syndromic, is carried out through a multidisciplinary team comprising: anesthesiology, pediatric surgery, general medicine, echocardiography, genetics, intensive medicine, neurosurgery, nutrology, otorhinolaryngology, pediatrics, plastic surgery, dentistry, speech therapy, nursing, physiology, psychology, physiotherapy, nutrition and dietetics, pharmacy, clinical analysis, imaging diagnosis, social work and occupational therapy (Bauru, 2020). With the prevalence of craniofacial malformations, there was the Global Strategies to Reduce the Healthcare Burden of Craniofacial Anomalies project, which is a proposal from the World Health Organization (WHO) that highlights the importance of enhancing efforts and establishing priority needs in inpatient rehabilitation. Conferences held internationally have the main objective of defining areas of research investment, such as genetic-environment interaction, multifactorial aspects, treatment and prevention, and, in addition to collecting data for global registration (WHO, 2002). The care protocol ranges from welcoming the family to rehabilitation, as shown in Table 3.

Table 3. Care protocol at the Cleft Lip and Palate Treatment Center (CEFIL) at Hospital Nossa Senhora do Loreto in Rio de Janeiro (Carrer, 2019).

Age group	Procedure
Pregnant	• Welcoming the pregnant woman and her family; • Referral of the pregnant woman to a multidisciplinary consultation; • Assessment of exams together with family members; • Provide information about the etiology, treatment protocol and care after the baby's birth; • Clarification of doubts; • First guidance on breastfeeding.

First care for newborn	• Diagnosis of the type of CLP; • Guidance on oral hygiene and the importance of multidisciplinary monitoring; • Instructions regarding breastfeeding; • Indication of the manufacture of the Palate Obturator Prosthesis (POP) and usage guide; • Explanation regarding the posture during breastfeeding, duration of feedings and facilitating maneuvers.
0 to 6 months	• In the case of cleft lip, quarterly follow-up until rhinocheiloplasty is performed; • Investigation of the chronology of tooth eruption; • Monthly monitoring of the use of POP in patients with cleft palate until palatoplasty is performed.
6 months to 6 years	• Referral and follow-up with the pediatric dentist regarding the chronology of tooth eruption; • Control and evaluation of occlusion development; • Observe the need to attend consultations due to the risk of cavities.
6 years	• All patients with fissures that affect the alveolar process of the maxilla are evaluated for the indication of a secondary graft.
6 to 12 years	For patients requiring alveolar bone grafting:
	• Pre-grafting orthodontic preparation; • Secondary graft when the upper canine has 2/3 of the root formed. • Tertiary graft when the upper canine is erupted.
12 to 18 years old	• Corrective orthodontic treatment or ortho-surgical treatment.

5. DENTAL TREATMENT

Dentistry is present in the rehabilitation of patients from the first months of follow-up. As mentioned above, patients with syndromic or non-syndromic CLP tend to have diverse

dental complications, such as agenesis, microdontia, and gyroversion (Corrêa *et al*. 2017). Furthermore, according to the surgical protocol (table 4), Dentistry is also responsible for composing the multidisciplinary team. Cleft patients are more prone to caries, not due to the presence of the cleft, but due to the existence of cofactors that favor the formation and development of biofilm, for example: the morphological and structural changes in the dentition and upper dental arch, make removal of bacterial plaque more difficult. Linked to this fact, there is the surgical scar, derived from primary surgeries, and upper lip tension, which end up restricting brushing. For these reasons, pediatric dentists are renowned in rehabilitation (Dalben *et al*., 2009).

Table 2. Surgical protocol in patients with CLP (Carrer, 2019).

AGE GROUP	Surgical Procedures
3 TO 6 MONTHS	• Rhinocheiloplasty in patients with pre-incisive foramen fissure; • Rhinocheiloplasty + Anterior Palatoplasty (Vomer flap) in patients with transforamen incisor cleft.
12 TO 18 MONTHS	• Palatoplasty in patients with post-incisive foramen cleft.
4 TO 6 YEARS	• Lip and/or nose revision in patients with pre-incisive foramen cleft; • Correction of oronasal and nasoalveolar fistulas in patients with pre-foramen or transforamen fissures; • Palate revision (velopharyngeal insufficiency) in patients with post-foramen or transforamen incisive cleft.
7 TO 9 YEARS	• Secondary alveolar bone grafting in patients who affect the lip and have impaction of the premaxilla, for example: if it is bilateral with unevenness of the premaxilla.
AFTER 16 YEARS	• Orthognathic surgery; • Structured Rhinoplasty.

6. DISCUSSION

A Van der Woude syndrome is the main syndrome associated with cleft lip and palate (Omim, 2014; Trevilatto & Werneck, 2014), is associated to with clinical signs such as hypodontia, numerary dental anomaly, characterized by the absence of a maximum of

six teeth(Capelão *et al*., 2013; Queiroga *et al*.,2016), in addition to cleft lip and palate and lip pits (Van Der Woude, 1954; Wervenka *et al*., 1967; Warbrick *et al*., 1951). Observing these characteristics is a form of clinical diagnosis (Queiroga *et al*., 2016), however, it is important to carry out the differential diagnosis in cases of ambiguity (Sanchis-Calvo *et al*., 2006). Therefore, Meggiolaro *et al*., 2020 explain that counseling and genetic investigation should be recommended to finalize the diagnosis.

As a result of CLP, patients present a series of anatomical variations in the lip, alveolar process, maxilla, palatine bones, and soft palate (*Spina et al*., 1972). Changes in the palate directly influence the fixation of muscle fibers, which are located in the median raphe, causing adequate muscular traction of the soft palate (Manzi *et al*., 2013). This traction dysfunction leads to recurrent middle ear otitis in these patients, since the contraction functions, during swallowing, cannot efficiently regulate the pressure inside the ear, which can cause, in more severe cases, loss of auditory (Sheahan *et al*., 2003; Oliveira *et al*., 2013).

Due to the extensive treatment and diverse phenotypes, a multidisciplinary and interdisciplinary team is notable in the rehabilitation process (Bauru, 2020; Carrer, 2019; WHO, 2002). Dentistry is present from the first consultations due to disorders: agenesis, microdontia, and gyroversion, in addition to the surgical area, such as Orthognathic surgery (Corrêa *et al*. 2017; Carrer, 2019).

7. CONCLUSION

According to Online Mendelian Inheritance in Man (OMIM) (2014), Van der Woude Syndrome is the main syndrome associated with Cleft Lip and Palate. When a congenital labial pit is evident in a patient, the most recommended intervention is a thorough anamnesis correlated with genetic counseling. The diagnosis of Van der Woude syndrome can be made clinically and confirmed by a geneticist, based on the presence of typical signs and in complementary exams. Rehabilitation is a long-term process carried out through a multidisciplinary team, composed of oral and maxillofacial surgery, pediatric surgery, plastic surgery, dentistry, nursing, physiology, physiotherapy, speech therapy, genetics, nutrition, otorhinolaryngology, psychology, and social work, to able to achieve satisfactory results. Therefore, it is clear and essential that the professional knows how to recognize the presence of Van der Woude syndrome so that it is possible to make a diagnosis, and an appropriate treatment plan and guide family members and the patient accurately.

Van der Woude Syndrome has multiple phenotypes and a low prevalence in the population, therefore due to its high genetic penetrance, variable expressivity, and autosomal

dominant heredity, detailed monitoring of the clinical case is necessary, so that there is completeness and humanization in the treatment, aiming at rehabilitation, to minimize future anatomical morphofunctional changes and, mainly, mitigate the sequelae of the syndrome.

REFERENCES

ALLORI, AC; MULLIKEN, JB; MEARA, JG; SHUSTERMAN, S.; MARCUS, JR Classification of Cleft Lip/Palate: Then and Now. Cleft Palate Craniofac J., v. 54, no. 2, p. 175-188, Mar. 2017.

BAURU. Cleft lip and palate. University of Sao Paulo. Hospital for rehabilitation of craniofacial anomalies. 2020. Available at: http://hrac.usp.br/saude/fissura-labiopalatina/. Accessed on: 28 June. 2020.

BUENO, MRP *et al*. Syndromic and non-syndromic cleft lip and palate. University of Sao Paulo. Human Genome and Stem Cell Research Center. 2015. Available at:https://genome.ib.usp.br/pt-br/servicos/consultas-e-testes-geneticos/doencas-atendidas/fissuras-labiopalatinas-sindromicas-e-nao-sindromicas. Accessed on: 28 June. 2020.

CAPELÃO, ACF et al. C-6. Hypodontia: about a clinical case. Portuguese Journal of Stomatology, Dental Medicine and Maxillofacial Surgery, v. 54, p. e42, 2013.

CARRER, FCA SUS and Oral Health in Brazil: for a future with reasons to smile. São Paulo: USP School of Dentistry, 2019.

WERVENKA, J. *et al*. The syndrome of pits of the lower lip and cleft lip and/or palate. Genetic considerations. American journal of human genetics, vol. 19, no. 3 Pt 2, p. 416, 1967.

CORRÊA, APS *et al*. Dental anomalies in patients with cleft lip and palate: a radiographic study. Brazilian Dental Archive, v. 11, no. 1, p. 20-25, 2017.

DALBEN, GS *et al*. Treating children with cleft lip and palate: special needs and attention required during dental care. In: Taggart, JC Handbook of dental care: diagnostic, preventive and restorative services. Hauppauge: Nova Science publishers, p. 199-266, 2009.

DESHPANDE, AS & GOUDY, SL Cellular and molecular mechanisms of cleft palate development. Laryngoscope Investigative Otolaryngology, v.4, n.1, p. 160-164, 2019.

KOPKO, G. Health Blog. In Brazil, one child is born with cleft lip and palate for every 650 births. 2016. Available at: http://www.blog.saude.gov.br/index.php/materias-especiais/51968-materia-especial-no-brasil-nasce-uma-crianca-com-fissura-labiopalatinas-a -every-650-births/. Accessed on: 29 June. 2020.

KUCHLER, E.C.Association between cleft lip and palate and the AXIN2 and IRF6 genes. Thesis (Doctorate in Medical Sciences).Faculty of Medicine, Federal Fluminense University. Niterói, p. 100, 2010.

MANZI, FR *et al*. The relationship between temporomandibular dysfunction and tubal dysfunction in patients with cleft palate. CEFAC Magazine, v. 15, no. 3, p. 509-615, 2013.

MEGGIOLARO, EDA*et al*. The Evolution of Treatment and Rehabilitation of a Patient with Van Der Woude Syndrome. In: FREITAS, Guilherme Barroso Langoni de.Pediatrics: professional experiences and case reports. Irati: Pasteur, 2020. Chapter 6. p. 52-69. Available at: https://doi.org/10.29327/522778. Accessed on: 12 Nov. 2020.

OLIVEIRA, MHMF Hearing changes in children with cleft lip and palate.Medical Journal of Minas Gerais, v. 23, p. 27-33, 2013.

ONLINE MENDELIAN INHERITANCE IN MAN. Van Der Woude Syndrome, 2014. Available at: https://omim.org/entry/119300?search=van%20der%20woude&highlight=der%20van%20woude. Accessed on: 26 June. 2020.

ORPHANET. Van Der Woude Syndrome. 2020. Available at: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=pt&Expert=888. Accessed on: 29 June. 2020.

ORTIZ-POSADAS, MR; VEGA-ALVARADO, L.; MAYA-BEHAR, J. A new approach to classify cleft lip and palate. Cleft Palate Craniofac J., v. 38, no. 6, p. 545-550, nov. 2001.

QUEIROGA, J. *et al*. Van der Woude syndrome: the purpose of a clinical case. Brazilian journal of stomatology, dentistry and maxillofacial surgery, v. 57, p. 8, 2016.

RODRIGUES, R.; FERNANDES, MH; MONTEIRO, AB; FURFURO, R.; SEQUEIRA, T.; SILVA, CC; MANSO, MC SPINA classification of cleft lip and palate: A suggestion for a complement. Arch Pediatr., v. 25, no. 7, p. 439-441, Oct. 2018.

SANCHIS CALVO, A. *et al*. Van der Woude syndrome. Minutes pediatric. esp, p. 396-398, 2006.

SHEAHAN, P. *et al*. Incidence and outcome of middle ear disease in cleft lip and/or cleft palate. International journal of pediatric otorhinolaryngology, v. 67, no. 7, p. 785-793, 2003.

SILVA FILHO, OG *et al*. Classification of cleft lip and palate: brief history, clinical considerations and suggested modification. Brazilian Journal of Surgery, v. 82, n.2, p. 59-65, 1992.

SPINA, V. A proposed modification for the classification of cleft lip and cleft palate. Cleft Palate J., v. 10, no. 6, p. 251-252, jul. 1973.

SPINA, V. *et al*. Classification of cleft lip and palate. Hospital das Clínicas Magazine of the Faculty of Medicine, v. 27, no. 2, p. 5-6, 1972.

SPINA, V.; PSILLAKIS, JM; LAPA, FS; FERREIRA, MC Classification of cleft lip and cleft palate. Suggested changes. Rev Hosp Clin Fac Med Sao Paulo, v. 27, no. 1, p. 5-6, Jan./Feb. 1972.

TEIXEIRA, LMS *et al*. Anatomy applied to dentistry. Guanabara Koogan, Rio de Janeiro, v. 2, 2008.

TESSIER, P. Anatomical classification facial, cranio-facial and latero-facial clefts. J Maxillo-fac Surg, vol. 4, no. 2, p. 69-92, 1976.

TREVILATTO, PC & WERNECK, RI Dental genetics. Abeno Series: Essential Dentistry - Basic Part. São Paulo: Artes Médicas, p.160, 2014.

VAN DER WOUDE, A. Fistula labii inferioris congenita and its association with cleft lip and palate. American journal of human genetics, vol. 6, no. 2, p. 244-56, 1954

WARBRICK, JG *et al*. Comments on the theology of congenital bilateral lower lip fistula. British Journal of Plastic Surgery, v. 4, p. 254-262, 1951.

WORD HELTH ORGANIZATION. Global strategies to reduce the health-care burden of craniofacial anomalies. Geneva: Word Health Organization, 2002.

CHAPTER IX

SYNDROMES OF DENTAL INTEREST: WILLIAMS-BEUREN SYNDROME

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ABSTRACT

Williams Syndrome (SW), also known as Williams-Beuren Syndrome (SWB) is a rare congenital syndrome, the condition being characterized as a series of physical and developmental abnormalities. The individual may have heart disease, vascular conditions, facial dysmorphism, endocrine, ophthalmic, audiological, and dental disorders, among others. Clinical findings and cytomolecular techniques make the diagnosis. The treatment of WBS is symptomatic, and individualized and must be performed by a multi-disciplinary team.

Keywords: Williams-Beuren syndrome, Dentistry, Dental treatment.

1. INTRODUCTION

Williams Syndrome (WS), also known as Williams-Beuren Syndrome (WSB), was first described by Dr. JCP Williams in 1961 in New Zealand, as a rare congenital syndrome in association with supravalvular aortic stenosis, mental deficiency and characteristic facial formation. in 04 children (Williams, 1961). Independently, in Germany in 1962, expanded the phenotype to include stenosis of the peripheral pulmonary arteries and dental malformations (Beuren *et al*., 1962).

The etiological factors of WBS are genetic, and the condition is characterized as a series of physical and developmental anomalies caused by a hemizygous microdeletion of approximately 26 to 28 genes on chromosome 7, band 7q11.23 (Francke, 1999). Although it may be an inherited syndrome, its origin is random in most cases and without preference for ethnicity or sex (Dutra *et al*., 2011).

Although the true incidence is unknown, the estimated number of WS cases is between 1 in every 20,000 and 50,000 live births worldwide (Trajan *et al*., 2003). However, the incidence may be even higher due to underdiagnosis due to the wide spectrum of anomalies and phenotypic variability of this condition (Ashkenas, 1996).

2. CLINICAL MANIFESTATIONS AND DIAGNOSIS

The systemic characteristics that can be found in WBS are heart disease and vascular conditions, with supravalvular aortic stenosis being the most common, but also arterial hypertension, ventricular septal defect and renal artery stenosis. In the urinary and endocrine system, recurrent infections and enuresis, obesity, diabetes and hyperthyroidism can occur and in relation to calcium metabolism in the body, there can be hypercalcemia

and hypercalciuria. Individuals with WBS may also present ophthalmic and audiological conditions such as strabismus, refraction problems, hypersensitivity to noise and ear infections. Cognitive and behavioral problems may be present such as intellectual and developmental disabilities, hyperactivity and generalized anxiety. They also present other signs such as scoliosis, sloping shoulders, relatively short limbs, clinodactyly (radial angulation to the palmar plane in an interphalangeal joint), hallux valgus, and soft skin (Pober, 2010; Poormina *et al*., 2012; Campos-Lara *et.al*., 2012; Strafacci, 2020).

Facial characteristics present with dysmorphism, present even if subtly, with variations, in all individuals with WBS, with the patient commonly presenting a long nasal philtrum, wide mouth and thick lips, small chin, depressed nasal bridge, wide eyebrows, increased periorbital volume, full cheeks, anteverted nostrils and starry iris, spiky or curly hair, among others. There are small changes in these characteristics over time and a greater demarcation of these in adults (Morris *et al*., 1988; Pober, 2010; Poormina *et al*., 2012; Andrade *et al*., 2015).

Concerning dental manifestations there may be the presence of morphological anomalies, prolonged retention of primary teeth, generalized diastema, enamel hypoplasia, crowding, microdontia and conoid or "screwdriver"-shaped incisors, taurodontism; unsatisfactory occlusion, pulp calcifications and high prevalence of cavities (Pober, 2010; Campos-Lara, 2012; Poormina *et al*., 2012; Wong *et al*., 2015; González-Sotelo *et al*., 2017; Castro *et al*., 2019).

The diagnosis of WBS is based on clinical findings and is generally made in childhood, when facial, cognitive characteristics, and cardiac findings are more evident (Lashkari *et al*., 1999). Diagnosis can also be made using cytomolecular techniques, such as fluorescence in situ hybridization (FISH), ligation-dependent multiple probe amplification (MLPA), and array-compared genomic hybridization (aCGH) (Pober, 2010).

3. TREATMENT

There is no cure for WBS and treatment is symptomatic and individualized. Early diagnosis is important as monitoring from childhood allows for good results in the patient's condition. It is interesting that patients are constantly monitored and that all treatment takes place under the supervision of a multidisciplinary team, made up of doctors, dental surgeons, physiotherapists, nutritionists, speech therapists, and others, professionals familiar with WBS (Twite *et al*., 2019).

Cognitive and behavioral manifestations must be treated early, with special education programs and physical, speech, and occupational therapies, and equine therapy can be considered added to these. The practice of basic functions should be recommended and contribute to the formation of a more functional adult individual. Physiotherapy, speech therapy and psychology professionals play an important role in this part of the treatment (Pober & Morris, 2007;Mervis & John, 2010). The use of psychotropic medications are also viable alternatives to the manifestation of hyperactivity, anxiety and other behavioral problems (Cherniske *et al*., 2004).

For heart disease present in patients, the existing alternatives are surgery and medication with lifelong monitoring of the patient's cardiovascular system. Surgical treatment of mitral valve insufficiency and stenoses can be performed, while hypertension is generally treated with calcium channel blockers (Pober & Morris, 2007; Collins *et al*., 2010).

Ophthalmic manifestations are treated with corrective techniques, whether surgical or not. AHyperopia is treated with the use of corrective lenses and strabismus with an eye patch or surgery. For dacryostenosis, which is total or partial obstruction of the tear duct, the use of antibiotic eye drops and local massages may be recommended. The manifestation-sAudiological disorders such as recurrent otitis can be treated with tympanostomy tubes. For hypersensitivity to noise, ear protection when exposed to strong noise is recommended (Pober & Morris, 2007; Pober, 2010; Twite *et al*., 2019; Morris *et al*., 2020).

The treatment of gastrointestinal problems depends on the patient's situation, be it reflux, hiatus hernia, diverticulitis or hypercalcemia. Colds should always be treated carefully at any age, due to the high risk of diverticulitis. The patient's diet should be rich in water and fiber. The treatment of hypercalcemia involves constant monitoring of calcium levels and it is recommended to increase water intake and follow up with a nutritionist so that the daily calcium intake from food is not greater than necessary. Regarding the endocrine conditions of patients with WBS, subclinical hypothyroidism does not require treatment but must be constantly monitored by an endocrinologist. Established hypothyroidism should be treated with thyroxine-based hormone therapy (Cherniskeet-Al., 2004; Pober & Morris, 2007; Pober, 2010; Twite *et al*., 2019; Morris *et al*., 2020).

4. DENTAL TREATMENT

The dental treatment of patients with WBS must be individualized according to the oral and systemic manifestations that each patient presents, with pediatric dentistry being the area of dentistry of great importance in these cases, considering that these manifesta-

tions must be treated early and monitored for life. of the patient (Ferreira *et al*., 2018 & Patil & Patil, 2021).

Cardiological conditions (predisposition to bacterial endocarditis, for example), endocrine, cognitive and behavioral conditions must be taken into consideration when providing care and planning the patient's treatment. Drug interactions, prophylactic antibiotic therapy, use of local or general anesthetics and the management of patient behavior during consultations must be carefully analyzed and the action of the multidisciplinary team is essential, especially contact between the responsible physician and the dental surgeon (Moskovitz, *et al*., 2005; Pober, 2010; Castro *et al*., 2019; Patil & Patil, 2021).

Audiological manifestations in patients with WBS, especially hypersensitivity to noise, can be a challenge in dental treatment and the management of these patients must be done carefully, aiming to avoid discomfort, fear and anxiety during treatment. Therefore, the use of ear protectors or headphones with relaxing music can be an ally, in addition to shorter consultations and behavior management with the "tell-show-do" technique (Pober, 2010; Poormina *et. al*, 2012; Castro *et al*., 2019; Patil & Patil, 2021).

For the treatment of generalized diastemas and unsatisfactory occlusion, common conditions in this type of patient, a joint assessment must be carried out with an orthodontist and analyze the feasibility of orthodontic treatment, taking into account what measures to take due to the possible presence of heterotropic dental anomalies such as retained deciduous teeth. and gyroversion, conditions also common in these patients (Ferreira *et al*., 2018; Castro *et al*., 2019; Patil & Patil, 2021).

Hypoplastic dental anomalies such as enamel hypoplasia, microdontia, conoid or "screwdriver-shaped" incisors and hyperplasia such as macrodontia and taurodontism can be treated by restorative and aesthetic dentistry. It is also necessary to pay attention to missing teeth so that rehabilitation with implants or prosthetics can be well planned and carried out early (Castro *et al*., 2019; Patil & Patil, 2021).

The high prevalence of cavities is also present in patients with WBS. In addition to family involvement and support, diet diaries, regular prophylaxis, application of fluoride, sealants and oral hygiene instructions should be part of dental treatment (Campos-Lara, 2012; Wong *et al*., 2015; González-Sotelo *et al*. , 2017; Patil & Patil, 2021).

5. DISCUSSION

WBS is a rare condition and the way it systematically affects the individual is highly variable. Manifestations of heart disease and kidney disorders are the main problems faced, in addition to the frequent presence of orofacial and dental anomalies (Pober, 2010; González-Sotelo *et al*., 2017; Ferreira *et al*., 2018).

The microdeletionhemizygous for approximately 26 to 28 genes on chromosome 7, band 7q11.23 encompasses the gene coding for elastin, which is a protein that works in the composition of the elastic fibers of connective tissue. This occurrence may explain some of the phenotypic characteristics present in WBS, such as heart disease, facial dysmorphism, hiatus hernias and joint problems, among others (Francke, 1999; Pober 2010; Kruszka *et al*. 2018; Strafacci *et al*., 2020).

Patients with WBS are more likely to develop reduced insulin sensitivity and poor glucose tolerance, which can occasionally progress to type 2 diabetes mellitus and therefore the dentist must pay attention to checking the glycemic level of these patients beforehand. consultations, when not so frequent (Axelsson *et al*., 2003 & Wong *et al*., 2015).

The oral health of patients with WBS through a coordinated and multidisciplinary approach should be one of the priorities throughout their treatment, especially considering the systemic conditions they already present and the possibility of infections that can cause serious problems, such as endocarditis. bacterial. In dental treatment, dental morphological anomalies can be treated by restorative and aesthetic dentistry and the absence of teeth is a factor that must be taken into consideration for the advance planning of prosthetics and implants. The choice of the most appropriate anesthetic procedures for each case must also be well planned (Castro *et al*., 2019 & Patil & Patil, 2021).

6. CONCLUSION

Considering the importance of this syndrome in the patient's life and the limitations it can bring, an early diagnosis is important so that the individual has the best treatment available, aiming for quality of life and dignity. Cooperation between family and multidisciplinary team is essential and individualized systemic conditions and oral health must be priorities in patient care.

REFERENCES

ANDRADE, NS; SANTOS, C.; CASTRO, T.; GALLOTTINI, M. Medical considerations in the dental treatment of patients with Williams-Beuren syndrome - report of four clinical cases. Clin Lab Res Den. 2015; 21(2):115-121.

ASHKENAS, J. Williams syndrome starts making sense. Am J Hum Genet. 1996;59(4):756-761.

AXELSSON, S.; BJØRNLAND, T.; KJAER, I.; HEIBERG, A.; STORHAUG, K. Dental characteristics in Williams syndrome: a clinical and radiographic evaluation. Acta Odontol Scand. 2003;61:129-136.

BEUREN, AJ; APITZ, J.; HARMJANZ, D. Supravalvular aortic stenosis in association with mental retardation and certain facial appearance. Circulation. 1962;26:1235-40.

CAMPOS-LARA, P.; SANTOS-DIAZ, MA; RUIZ-RODRÍGUEZ, MS; GARROCHO--RANGEL, JA; POZOS-GUILLÉN, AJ Orofacial findings and dental management of Williams-Beuren syndrome. J Clin Pediatr Dent. 2012;36(4):401-404. doi:10.17796/jcpd.36.4.c93436771101tm06.

CASTRO, T.; SANTOS, CPM; ORTEGA, AOL; GALLOTTINI, M. Oral characteristics and medical considerations in the dental treatment of individuals with Williams syndrome. Special Care in Dentistry. 2019;39(2): 108-113. doi:10.1111/scd.12361.

CHERNISKE, EM; CARPENTER, TO; KLAIMAN, C.; YOUNG, E.; BREGMAN, J.; INSOGNA, K.; SCHULTZ, RT; POBER, BR Multisystem study of 20 older adults with Williams syndrome. Am J Med Genet A. 2004;131(3):255-264. doi:10.1002/ajmg.a.30400.

COLLINS 2ND, RT; KAPLAN, P.; SOMES, GW; ROME, JJ Long-term outcomes of patients with cardiovascular abnormalities and Williams syndrome. Am J Cardiol. 2010;105(6):874-878. doi:10.1016/j.amjcard.2009.10.069.

DUTRA, RL; PIERI, PC; TEIXEIRA, ACD; HONJO, RS; BERTOLA, DR; KIM, CA DETECTION of deletions at 7q11.23 in Williams-Beuren syndrome by polymorphic markers. Clinics. 2011;66(6):959–964. doi:10.1590/S1807-59322011000600007.

FERREIRA, SB; VIANA, MM; MAIA, NG; LEÃO, LL; MACHADO, RA; COLETTA, RD; DE AGUIAR, MJ; MARTELLI-JÚNIOR, H. Oral findings in Williams-Beuren syndrome. Med Oral Patol Oral Cir Bucal. 2018;23(1):e1-e6. doi:10.4317/medoral.21834.

FRANCKE, U. Williams-Beuren syndrome: genes and mechanisms. Hum Mol Genet. 1999;8:1947-54.

GONZÁLEZ-SOTELO, A.; MONTER-GARCÍA, MA; CONTRERAS-BULNES, R. Dental management in Williams-Beuren syndrome: Case report. Dental and Medical Problems. 2017; 54:201-204. doi:10.17219/dmp/68579.

KRUSZKA, P.; FUCKING, AIR; DE SOUZA, DH; MORESCO, A.; HUCKSTADT, V., et al. Williams–Beuren syndrome in diverse populations. Am J Med Genet A. 2018;176(5):1128-1136. doi: 10.1002/ajmg.a.38672.

LASHKARI, A.; SMITH, A.K.; GRAHAM, JMJR. Williams-Beuren syndrome: an update and review for the primary physician. Clin Pediatr. 1999;38:189-208.

MERVIS, CB; JOHN, AE Cognitive and behavioral characteristics of children with Williams syndrome: implications for intervention approaches. Am J Med Genet C Semin Med Genet. 2010;154C(2):229-248. doi:10.1002/ajmg.c.30263.

MORRIS, CA; BRADDOCK, SR; AAP COUNCIL ON GENETICS. Health Care Supervision for Children With Williams Syndrome. Pediatrics. 2020;145(2):e20193761. It hurts:10.1542/peds.2019-3761.

MORRIS, CA; DEMSEY, SA; LEONARD, CO; DILTS, C.; BLACKBURN, BL Natural history of Williams syndrome: physical characteristics. J Pediatr. 1988;113:318-326,

MOSKOVITZ, M.; BRENER, D.; FAIBIS, S.; PERETZ, B. Medical considerations in dental treatment of children with Williams syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;99(5):573-580. doi:10.1016/j.tripleo.2004.03.019.

PATIL, PM; PATIL, SP Williams–Beuren syndrome: a complete guide for oral healthcare. J Oral Med Oral Surg. 2021;27(2):1-21. doi: https://doi.org/10.1051/mbcb/2020060.

POBER, BR; MORRIS, CA Diagnosis and management of medical problems in adults with Williams-Beuren syndrome. Am J Med Genet C Semin Med Genet. 2007;145C(3):280-290. doi:10.1002/ajmg.c.30139.

POBER, BR Williams-Beuren syndrome. N. Engl. J Med 2010;362:239-252. doi: 10.1056/NEJMra0903074.

POORNIMA, P.; PATIL, PS; SUBBAREDDY, VV; ARORA, G. Dentofacial characteristics in William's syndrome. Contemp Clin Dent. 2012;3(Suppl 1):S41-S44. doi:10.4103/0976-237X.95103.

STRAFACCI, ASL; FERNANDES, JC; BERTAPELLI, F.; GUERRA JÚNIOR, G. Growth assessment in children with Williams-Beuren syndrome: a systematic review. J Appl Genet. 2020;61(2):205-212. doi:10.1007/s13353-020-00551-x.

TRAJAN, I.; BALATON, G.; BALATON, P.; VARBIRO, S.; VAJO, Z. Facial and dental appearance of Williams syndrome. Postgrad Med J. 2003;79(930):241. doi: 10.1136/pmj.79.930.241.

TWITE, MD; STENQUIST, S.; ING, RJ. Williams syndrome. Paediatr Anaesth. 2019;29(5):483-490. doi:10.1111/pan.13620.

WILLIAMS, JCP; BARRATT-BOYES, BG; LOVE, JB. Supravalvular aortic stenosis. Circulation. 1961;21:1311-8.

WONG, D.; RAMACHANDRA, SS; SINGH, AK. Dental management of patient with Williams Syndrome - A case report. Contemp Clin Dent. 2015;6(3):418-420. doi:10.4103/0976-237X.161908.

CHAPTER X

SYNDROMES OF DENTAL INTEREST: PIERRE ROBIN SYNDROME

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ABSTRACT

Pierre Robin Sequence (SPR) is a congenital craniofacial deformation characterized by micrognathia, glossoptosis, and upper airway obstruction (OVAS). Cleft palate occurs in up to 90.4% of cases. SPR can have syndromic associations or not. The most common associations are Stickler, velocardiofacial, craniofacial microsomia, and Treacher Collins, respectively. The hypotheses related to SPR include a primary failure of mandibular growth or a muscle defect with failure to lower the tongue. The most critical consequence of SPR is OVAS in the neonatal period, and in milder circumstances, it can be treated through conservative treatment such as continuous positive airway pressure, nasal cannula oxygen, prone positioning, and nasopharyngeal airways. Surgical procedures are generally reserved for patients who continue to present severe airway obstruction with hypoxemia and hypercapnia, they are tongue-lip adhesion, mandibular osteogenic distraction, and tracheostomy. Thus, the main point to be taken into account in SPR is OVAS and its complications. Conservative or surgical treatment to solve this problem should be done taking into account the risks inherent to patients, especially those with syndromic associations.

Keywords: Pierre Robin sequence, Upper airway obstruction, Mandibular osteogenic distraction, Modified palatal plate.

1. INTRODUCTION

The Pierre Robin sequence (PRS) is the result of a cascade of events that occur during embryological development, and can occur alone or as part of a syndrome (Hardwicke *et al*., 2016). The most common syndromic associations are respectively Stickler, velocardiofacial, craniofacial microsomia and Treacher Collins (Shen *et al*., 2012), in total they correspond to 38% to 44% of cases. The incidence of RPS varies from 1:5000 to 1:85,000, affecting men and women equally, this wide variation in the incidence of RPS may be caused by variability in clinical presentation (Cladis *et al*., 2014; Hsieh; Woo, 2019).

PRS is a congenital craniofacial deformity characterized by micrognathia, glossoptosis and upper airway obstruction (OVAS) (Li *et al*., 2020), although Robin's original 1923 description did not mention cleft palate, it occurs in up to 90.4 percent of cases (Hardwicke *et al*., 2016). Mortality of infants with RPS ranges from 1.7% to 11.3%, this rate increases to 26% when examining only the subset of syndromic patients (Hsieh; Woo, 2019).

2. CHARACTERISTICS OF THE SYNDROME

Hypotheses related to SPR include a primary failure of mandibular growth or a muscular defect with failure of tongue descent. The SOX9 gene, a critical chondrogenic factor, has been associated with non-syndromic RPS, supporting the theory of mandibular growth failure (Hardwicke *et al*., 2016). It is suspected that micrognathia keeps the tongue positioned superiorly between the naturally cleft palatal platforms and prevents normal palatal closure during the first trimester of pregnancy, resulting in the formation of a cleft palate *(Cladis et al*., 2014).

OVAS can have 4 causes: retroposition of the tongue and consequent compression against the posterior pharyngeal wall, retropositioning of the tongue and consequent compression of the soft palate against the posterior pharyngeal wall, collapse of the lateral pharyngeal wall and generalized collapse of the pharyngeal wall (Lee; Bradley, 2014). The first two causes would be due to glossoptosis, which is the backward and downward fall of the base of the tongue, while the posterior wall of the pharynx remains in a stationary position (Schweiger; Manica; Kuhl, 2016). The last two causes are sequelae resulting from micrognathia, the more severe the micrognathia, the more serious the collapse (Cladis *et al*., 2014). If left untreated, OVAS can lead to chronic hypoxemia, carbon dioxide retention, pulmonary hypertension and, ultimately, failure to thrive (Shen et al., 2012), clinically patients may present stridor, retractions, and cyanosis (Cladis *et al*., 2014).

Children with non-syndromic RPS, when compared to normal children, have significantly shorter mandibular length in early childhood and adolescence, and maxillary hypoplasia in adolescence, this presents with the convexity of the facial profile (Shen *et al*., 2012), which contradicts the concept of catch-up growth of the mandible. This concept states that the mandible in patients with RPS has the potential to grow faster when compared to normal patients, thus resolving the maxillomandibular discrepancy inherent to the sequence. According to the systematic review of Purnell and collaborators (2019), a minority of objective studies suggest increased rates of mandibular growth in isolated SPR and even fewer studies suggest that maxillomandibular discrepancy in SPR resolves completely.

Respiratory problems are also related toeating and swallowing disorders, but they are not the only cause. Gastroesophageal reflux (GER) is a known comorbidity of PRS, probably caused by altered intrathoracic pressures secondary to OVAS. The clinical consequences of GER include aspiration, pharyngeal and laryngeal edema, which contribute

to OVAS. Due to the incidence and consequences of reflux, most doctors recommend prophylactic medical treatment (Cladis *et al*., 2014).

3. DIAGNOSIS

Complications of OVAS can be avoided with early and appropriate treatment, resulting in good results in eating, speech and facial profile (Linz *et al*., 2011). Ultrasound examination of the fetus is currently the current standard for prenatal care and the primary imaging modality for screening and diagnostic purposes, but because RPS is based on clinical findings, it cannot be definitively diagnosed until delivery and birth. proof of airway involvement (Kaufman *et al*., 2016).

4. TREATMENT

The newborn and infant with RPS require a multidisciplinary approach comprised of a team including anesthesiology, plastic surgery, otolaryngology, speech pathology, gastroenterology, radiology and neonatology (Cladis *et al*., 2014; Kocaaslan *et al*., 2020).

Conservative treatment

The most critical consequence of RPS is OVAS in the neonatal period (Lee; Bradley, 2014). In the mildest circumstances it can be treated by non-surgical interventions: continuous positive airway pressure, oxygen via nasal cannula, prone positioning and nasopharyngeal airways (Shen *et al*., 2012; Cladis *et al*., 2014; Almajed *et al*., 2017; Tomic *et al*., 2020). In general, babies with nonsyndromic RPS do better with conservative measures, as long as their airway is stable with positioning and they are feeding and gaining weight appropriately (Khansa *et al*., 2017). The symptoms of OVAS disappear as the baby grows, due to the increase in the size of the airways, better control of the tongue muscles and jaw growth (Shen *et al*., 2012; Cladis *et al*., 2014).

The modified palatal platewith velar extension is a non-surgical approach option for OVAS in syndromic and non-syndromic RPS. The palatal plate covers any potential cleft palate and widens the hypopharynx. Meanwhile, velar extension displaces the tongue anteriorly so that the OVAS is adequately relieved. The device is worn for most of the day and eventually removed after several months as the baby's respiratory status improves. They are held in situ with the help of a fixative cream and extraoral wire loops attached to the child's face with adhesive tape (Poets *et al*., 2019; Tomic *et al*., 2020).

Surgical treatment

The surgical procedures are: tongue-lip adhesion (ALL), mandibular distraction osteogenesis (DOM) and tracheostomy. They are generally reserved for patients who continue to experience severe airway obstruction with hypoxemia and hypercapnia (Shen *et al*., 2012).

Airway interventions should be performed only after nasoendoscopy and bronchoscopy to delineate sites of airway compromise beyond the base of the tongue, as patients with subglottic anomalies may be poor candidates for distraction and should undergo tracheostomy (Hsieh; Woo, 2019). The main concern in the postoperative management of patients with PRS is OVAS, which can result in hypoxia, negative pressure pulmonary edema, and death. Patients with RPS are particularly prone to postoperative respiratory complications from OVAS for several reasons, including prior airway obstruction, opioid sensitivity, and surgically induced airway edema (Cladis *et al*., 2014).

Tongue-lip adhesion

All surgically attaches the tongue to the lingual surface of the lower lip by suturing the genioglossus muscle to the orbicularis oris muscles, forcing the tongue anteriorly and inferiorly (Cladis *et al*., 2014). Its advantages include its relative technical simplicity and a reported success rate of 71% to 89%. Complications include adhesion dehiscence and the need for additional procedures. The greater success and lower complication rates in non-syndromic patients reinforce the importance of appropriate patient selection and consideration of other techniques in patients with associated syndromic diagnoses (Viezel-Mathieu; Safran; Gilardino, 2016; Diep; Eisemann; Flores, 2020;).

Mandibular distraction osteogenesis (DOM)

The modern application of distraction osteogenesis to lengthen the neonatal mandible and directly treat OVAS is still evolving (Cladis *et al*., 2014). The general concept of DOM begins with an initial osteotomy followed by linear mechanical force from the distraction device that serves to direct bone formation. There are various osteotomy designs, surgical tools, distraction devices, and distraction protocols, requiring individualized assessment and work on each patient (Lee; Bradley, 2014; Diep; Eisemann; Flores, 2020). The gradual advancement of the jaw and tongue forward increases pharyngeal space, relieving dyspnea and feeding difficulties (Li *et al*., 2020). Reported complications of DOM involve relapse, nerve injury, tooth injury, infection, incorrect distraction vector, and device failure (Lee; Bradley, 2014).

In children, orthodontic treatment alone can achieve functional occlusion in most cases, although surgery may be indicated to address functional or aesthetic issues. Genioplasty can improve chin projection and reduce anterior facial height to improve aesthetics. If there are functional problems such as OVAS, surgical advancement of the maxilla and mandible may be necessary (Shen *et al*., 2012).

Long-term growth of the mandible in patients with Pierre Robin sequence treated conservatively may remain deficient, thus requiring surgical correction at skeletal maturity. A high proportion of skeletally mature Pierre Robin sequence patients undergo orthognathic surgery, in more than half of cases with mandibular advancement (Pfaff *et al*., 2020).

Palatoplasty

There is no general consensus on the timing or surgical technique for cleft palate closure in these patients, but in all cases preoperative screening with a polysomnography as well as a general check-up and history is important for monitoring these conditions. patients. Furthermore, every surgeon must be aware of the risk of OVAS after palatoplasty (Opdenakker *et al*., 2017). Speech 5 years after cleft palate repair is worse in children with Pierre Robin sequence than in a cleft-matched non-Pierre Robin sequence comparison group. Parents should be advised that speech development may be worse than in other children with cleft palate and will be at significantly higher risk of secondary speech surgery (Hardwicke *et al*., 2016).

5. DISCUSSION

Early and adequate treatment is essential to obtain good results in eating, speech, and facial profile. To this end, an ultrasound examination of the fetus is the primary imaging modality for screening and diagnostic purposes, although PRS can only be definitively diagnosed after airway involvement has been proven (Linz *et al*., 2011; Kaufman *et al*., 2016;).

Normally babies with non-syndromic RPS improve with conservative measures due to increased airway size, better control of tongue muscles and jaw growth (Shen *et al*., 2012; Cladis *et al*., 2014;). The use of the modified palatal plate with extension also offers great help in controlling OVAS in the first months of life if used (Poets *et al*., 2019; Tomic *et al*., 2020). However, long-term growth of the mandible in patients with Pierre Robin sequence treated conservatively may remain deficient, requiring orthognathic surgery after skeletal maturity. It is possible that the presence of a cleft palate, and its repair, in some patients with

RPS mitigates maxillary growth, thus creating the illusion of a normal maxillomandibular relationship (Pfaff *et al*., 2020), which contributes to the study of purnell and collaborators (2019), where increased rates of mandibular growth in isolated SPR and resolution of maxillomandibular discrepancy in SPR are rarely found. In any case, the selection of patients for surgical treatment must be done with caution, as patients with PRS are particularly prone to postoperative respiratory complications of OVAS, especially cases with syndromic association, as they have a lower success rate and higher complication rates (Cladis *et al*., 2014; Viezel-Mathieu; Safran; Gilardino,2016; Diep; Eisemann; Flores, 2020). Patients with RPS also have a worse speech prognosis after palatoplasty and a greater chance of needing secondary surgery when compared to children without it (Hardwicke *et al*., 2016).

6. CONCLUSION

The main point to be taken into account in SPR is OVAS and its complications. Conservative or surgical treatment to resolve this problem must be carried out taking into account the risks inherent to patients, especially those with syndromic associations. Long-term results must also be taken into account, as it may be necessary to perform future surgical procedures if a procedure is not performed early.

REFERENCES

ALMAJED, A. *et al*. Outcome Following Surgical Interventions for Micrognathia in Infants With Pierre Robin Sequence: A Systematic Review of the Literature. The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association, vol. 54, no. 1, p. 32–42, 2017.

CLADIS, F. *et al*. Pierre Robin Sequence: a perioperative review. Anesthesia and Analgesia, vol. 119, no. 2, p. 400–412, Aug. 2014.

DIEP, GK; EISEMANN, BS; FLORES, RL. Neonatal Mandibular Distraction Osteogenesis in Infants With Pierre Robin Sequence. The Journal of Craniofacial Surgery, vol. 31, no. 4, p. 1137–1141, jun. 2020.

HARDWICKE, JT *et al*. Outcomes of Cleft Palate Repair in Patients with Pierre Robin Sequence: A Matched Case-Control Study. Plastic and Reconstructive Surgery, vol. 137, no. 3, p. 927–935, mar. 2016.

HSIEH, ST; WOO, AS Pierre Robin Sequence. Clinics in Plastic Surgery, vol. 46, no. 2, p. 249–259, apr. 2019.

KAUFMAN, MG *et al*. Prenatal Identification of Pierre Robin Sequence: A Review of the Literature and Look towards the Future. Fetal Diagnosis and Therapy, vol. 39, no. 2, p. 81–89, 2016.

KHANSA, I. *et al*. Airway and Feeding Outcomes of Mandibular Distraction, Tongue-Lip Adhesion, and Conservative Management in Pierre Robin Sequence: A Prospective Study. Plastic and Reconstructive Surgery, vol. 139, n. 4, p. 975e–983e, apr. 2017.

KOCAASLAN, FND *et al*. The Comparison of Pierre Robin Sequence and Non-Syndromic Cleft Palate. The Journal of Craniofacial Surgery, vol. 31, no. 1, p. 226–229, Feb. 2020.

LEE, JC; BRADLEY, JP. Surgical considerations in pierre robin sequence. Clinics in Plastic Surgery, vol. 41, no. 2, p. 211–217, apr. 2014.

LI, J. *et al*. Dynamical Changes of Mandible and Upper Airway After Mandibular Distraction Osteogenesis in Pierre Robin Sequence. The Journal of Craniofacial Surgery, vol. 31, no. 2, p. 513–516, apr. 2020.

LINZ, A. *et al*. Pierre Robin Sequenz: Pränatale Diagnostik und interdisziplinäre Therapie. Zeitschrift für Geburtshilfe und Neonatologie, v. 215, no. 03, p. 105–108, jun. 2011.

OPDENAKKER, Y. *et al*. Postoperative Respiratory Complications After Cleft Palate Closure in Patients With Pierre Robin Sequence: Operative Considerations. The Journal of Craniofacial Surgery, vol. 28, no. 8, p. 1950–1954, Nov. 2017.

PFAFF, MJ *et al*. Long-Term Orthognathic Considerations in the Pierre Robin Sequence Patient. Plastic and Reconstructive Surgery, vol. 146, no. 5, p. 599e–606e, 2020.

POETS, CF *et al*. The Tübingen palatal plate approach to Robin sequence: Summary of current evidence. Journal of Cranio-Maxillo-Facial Surgery: Official Publication of the European Association for Cranio-Maxillo-Facial Surgery, v. 47, no. 11, p. 1699–1705, nov. 2019.

SCHWEIGER, C.; MANICA, D.; KUHL, G. Glossoptosis. Seminars in Pediatric Surgery, vol. 25, no. 3, p. 123–127, jun. 2016.

SHEN, YF *et al*. Facial skeletal morphology in growing children with Pierre Robin sequence. The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association, vol. 49, no. 5, p. 553–560, Sept. 2012.

TOMIC, J. *et al*. Weight gain in infants with Pierre Robin sequence. Journal of Cranio-Maxillo-Facial Surgery: Official Publication of the European Association for Cranio-Maxillo-Facial Surgery, v. 48, n. 6, p. 555–559, jun. 2020.

VIEZEL-MATHIEU, A.; SAFRAN, T.; GILARDINO, MS A Systematic Review of the Effectiveness of Tongue Lip Adhesion in Improving Airway Obstruction in Children With Pierre Robin Sequence. The Journal of Craniofacial Surgery, vol. 27, no. 6, p. 1453–1456, Sept. 2016.

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SYNDROMES AFFECTING CRANIOFACIAL AND DENTAL STRUCTURES

The curricular component of Syndromes Affecting Craniofacial and Dental Structures provides students and teachers with scientific foundations associated with anthropological, technical, and artistic aspects.

There are numerous methodologies to approach the teaching of Syndromes Affecting Craniofacial and Dental Structures. In this book, the content was distributed across ten chapters, ending with a step-by-step overview of the main syndromes Affecting Craniofacial and Dental Structures. The sequence of chapters and their contents were arbitrarily determined, aiming at a didactic presentation logic, for professionals and students who make this profession a mixture of art and science. Since dental practice in the current situation needs to be based on scientific evidence.

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