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Oral Manifestations of Hunter Syndrome: The Role of The Dentist in The Diagnosis of Mucopolysaccharidosis

Nathalie Steffy Ponce Reyes, Miryan Margarita Grijalva Palacios, Luis Fernando Andrade Andrade, Kevin Alexander Chandi Chauca

Universidad Regional Autónoma de Los Andes, Sede Ibarra, Ecuador.

Corresponding Author: Nathalie Steffy Ponce Reye
E-mail: ui.nathaliepr73@uniandes.edu.ec, ui.miryangp00@uniandes.edu.ec, luisfaa92@uniandes.edu.ec, kevincc19@uniandes.edu.ec

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Abstract

The objective of this research is to describe the oral and dental manifestations of Hunter syndrome. A systematic review was carried out, which at a methodological level has the PRISMA procedure, where 25 original articles related to the research topic were considered. Three academic databases were used in the search analysis: Google Scholar, Pubmed and Scielo. The results obtained lead to the conclusion that the oral-dental manifestations in patients with Hunter syndrome begin to be observed from the age of 2 years, so the prevalence at this age should trigger a warning sign to the treating dentist in order to develop preventive education aimed at fathers, mothers or representatives in charge of the child who presents this pathology so that good oral-dental care is provided; however, different multidisciplinary techniques for care should be investigated.

Keywords: Mucopolysaccharidosis; Hunter Syndrome; Iduronate Sulfatase; Glycosaminoglycans; Oral manifestations.

Introduction

Hunter syndrome or mucopolysaccharides (MPS) is a genetic disease, caused by the absence of the enzyme Iduronate-2-sulfatase, whose main function is the breakdown of mucopolysaccharides, to prevent their accumulation (1).

It is a pathology that has a higher incidence in boys, who begin to present symptoms between 2 and 4 years of age, presenting at an early stage, therefore, its diagnosis is complicated. It is progressive and degenerative, as it will present complications in the correct activity of cells, tissues and organs (2). Early diagnosis of Hunter Syndrome in the dental area is important, since preventive treatments can be planned to reduce complications in this area, as well as correct planning based on the patient's needs.

In the dental aspect, it is taken into account that when presenting a deficiency of the enzyme Idurinate-2-sulfatase, it will have difficulties in the production of dental tissues, therefore, it will

present alterations in the part of the stomatognathic system from an early age, thus contributing to an early diagnosis of MPS, from the dental point of view (3).

The first morphological indication is the presentation of a brachyfacial biotype, with prominence in its features in the facial massif, which will have consequences in the area of swallowing, phonation and respiratory, in the same way, a square and wide jaw, delay in tooth eruption or incorrect position of the already erupted primary teeth is evidenced in simple features (4). (5).

In the maxillomandibular structure, the condyle will show a neck with less prominence than normal and the fossa on the contrary present's greater prominence than adequate, flat alveolar ridges, high arched palate and short mandibular ramus (4), (5).

After the above, the objective is to describe the oral manifestations of this syndrome that can occur at an early age, thus contributing to its early identification.

Materials and Methods

The methodology used was the use of the PRISMA method to carry out a systematic review of the literature related to the oral manifestations of Hunter Syndrome. The objective was to describe these manifestations in detail, the data collection technique used was the bibliographic review and a descriptive analysis of each of the contents of the 25 selected articles was carried out.

The data were collected from three academic databases: Google Scholar, PubMed and Scielo, the inclusion criteria for the selection of the articles were based on their relevance to the research topic, the articles included in the documentary corpus covered the period from 2018 to 2023.

The PRISMA method, used in this research, is a systematic approach that guarantees transparency and rigor in the selection of articles and the analysis of the results, thanks to this method, it was possible to consider a set of 25 original articles to carry out the systematic review.

Table 1 PubMed search strategy number of articles: 110

SEARCH TERMS IN 2018-2021	
1.	Mucopolysaccharidosis, Hunter Syndrome
2.	Iduronate 2-sulfatase, Oral manifestations
3.	Oral Health, Hunter Syndrome

Table 2 Search strategy in BVP number of articles: 137

PubMed Google Search Terms, Academic Scielo 2018-2021	
1.	Mucopolysaccharidosis, Hunter Syndrome
2.	Iduronate 2-sulfatase, Oral manifestations
3.	Oral Health, Hunter Syndrome

Table 3 Search strategy in Google Scholar number of articles:113

Search terms in PubMed Google, Scielo Scholar 2018-2021	
1.	Mucopolysaccharidosis, Hunter Syndrome
2.	Iduronate 2-sulfatase, Oral manifestations
3.	Oral Health, Hunter Syndrome

Results and Discussion

The following figure details the results obtained after selecting and analysing 366 research articles in different countries and within the period 2018-2021.

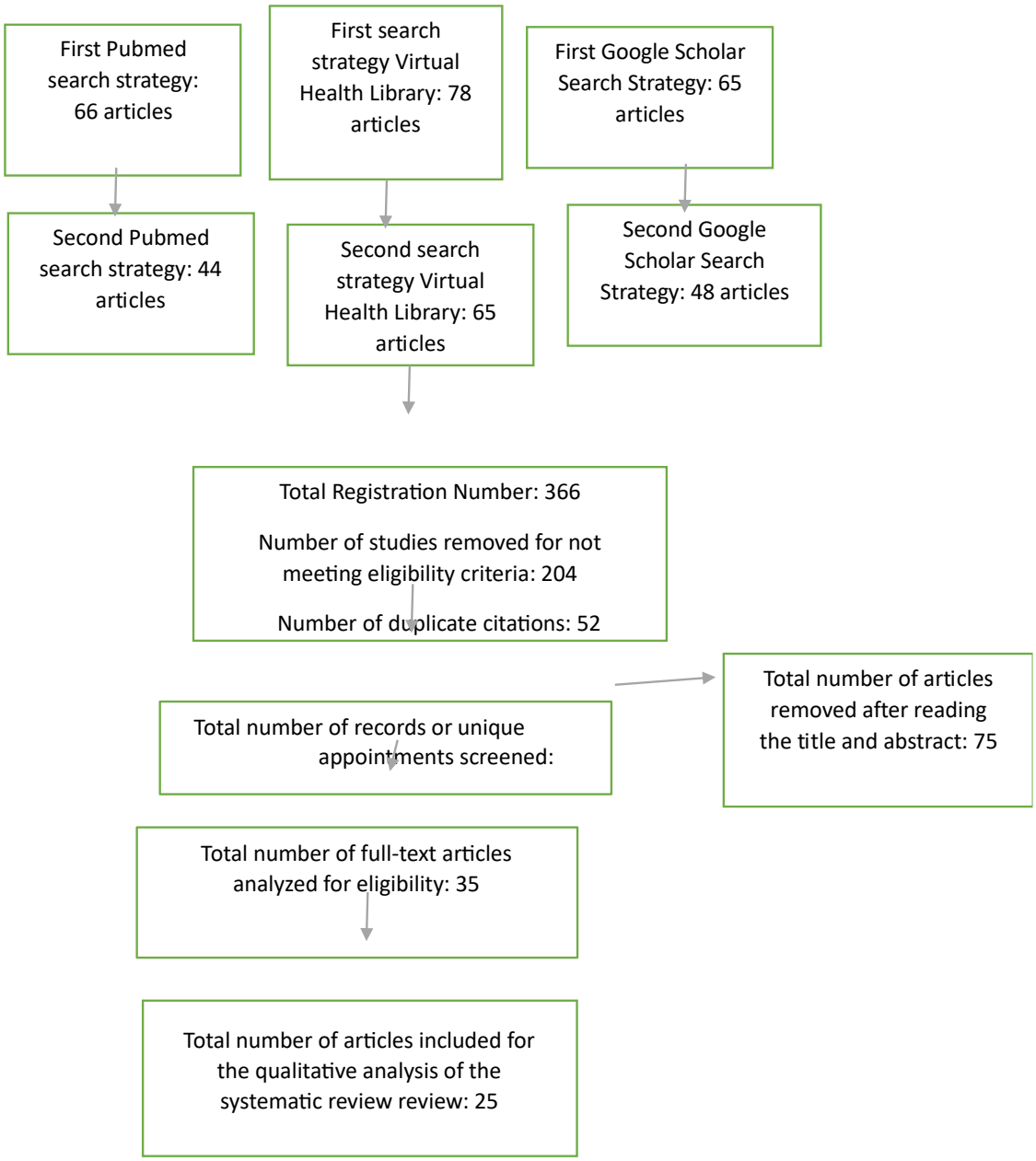

Figure 1 Diagram of the search and results process

Figure 1 shows the data collection and analysis technique, in which a total of 366 articles predominates, of which 204 were discarded by the eligibility criterion and 52 by duplicate citations. Obtaining a result of 110 articles screened by citations.

During the search for the title and abstract, a total of 75 articles were excluded, thus limiting a total of 25 articles eligible for inclusion in the present study, the 25 articles in this systematic review will serve as a basis for the quantitative synthesis.

N	Author	Title	Data	Category
1	Oliveira Torres, Andrea Vaz B. 2018	Three-Dimensional Dental and Craniofacial Manifestations in Patients With Late Diagnosis of Mucopolysaccharides Type II: 2 Case Report	Patients were evaluated clinically (soft tissue assessment, occlusion assessment, periodontal and dental examinations) and by craniofacial computed tomography, with three-dimensional image evaluation.	Three-dimensional images and overlays revealed oral and skeletal displacements.
2	Annelies e L, Dafne Dain G. 2018	Oral and Craniofacial Manifestations in a Hunter Syndrome Patient With Hematopoietic Stem Cell Transplantation: Report of a Case	The absence of treatments for MPS and the high cost of enzyme therapy motivate researchers to continue developing new therapeutic alternatives	The main oral clinical signs were: macroglossia, posterior crossbite, crowding.

3	Amira Abdelhefeez E. 2022	Improving the oral health-related quality of life of a child with Hunter syndrome: a case report and literature review	Severe metabolic disorder with heterogeneous multisystem manifestations including oral features. It is very important to raise awareness of couples with a history of family members with genetic diseases	Importance of proper referral and treatment of dental needs with Hunter Syndrome.
4	Andrea R, Mariana LLorensi. 2020	Manifestations Oral of patients with mucopolysaccharides	It is a lysosomal overload disease, characterized by the accumulation of mucopolysaccharides, associated with the deficit of the activity of an enzyme that catalyzes the degradation of GAGs, which causes an accumulation of them. Its accumulation in several organs alter their function.	Oral manifestations of MPS include flat alveolar ridges, hyperplastic gums, macroglossia, arched and high palate, short mandibular ramparts with abnormal condyles.
5	Andrea V, Mariana Llorensi R. 2018	Oral manifestations of patients with mucopolysaccharidosis	Several patients had various oral manifestations. For example, patients with MPS I presented with anterior open bite, dental gyroversion, diastemas, microdontia, enamel hypoplasias, macroglossia, and mouth breathing. In patients with MPS II, anterior open bite, posterior crossbite, dental gyroversion, diastemas, delayed eruption, gingival hyperplasia, macroglossia, enamel hypoplasias, microdontia, and mouth breathing were observed.	The majority of patients (90%) required dental treatment due to these oral manifestations. The most common manifestations observed were macroglossia (84.2%) and anterior open bite (79%).

			The patient with MPS type III presented with anterior open bite, diastemas, delayed rash, macroglossia, mouth breathing, and molar class II. In the case of MPS type IV A, similar characteristics were found, such as anterior open bite, diastemas, gingival hyperplasia, macroglossia, and molar class II.	
6	Scott D. Groose, Angela M. 2023	Evidence and Recommendations for the Detection of Type II Mucopolysaccharidosis in the United States	Urinalysis is helpful, but sometimes inaccurate. Radiographic examination may show characteristic bony abnormalities. Mucopolysaccharidosis is also diagnosed by analyzing blood cells.	X-linked condition, which is detected by x-ray examination or blood cell analysis
7	Chung Lin Lee. 2022	Diagnosis Confirmed Up-to-date For Mucopolysaccharidosis In Taiwanese Babies and the App Genetic Variants	Enzyme replacement therapy is used to treat some mucopolysaccharidosis and prevent the disorders from developing. Diagnosis is made through a series of quantitative measurements, including the concentration of GAGs in the urine.	One way to prevent the progression of the syndrome is enzyme substitution after diagnosis.

8	EA Nikolaev a. 2019	Clinical Case: Rare Case or Syndrome Of Hunter (Mucopolysaccharidosis type II) in a girl	The result of the syndrome is a characteristic facial appearance and abnormalities in the bones, eyes, liver, and spleen, sometimes accompanied by mental retardation, growth retardation, pain in the abdomen, and pain in the abdomen. lower limbs and joint stiffness.	The characteristics of Hunter syndrome are going to be present in the facial massif and in conjunction with mental retardation.
9	Francesca D'Avanzo, Laura R. 2020	Mucopolysaccharidosis Type II One Hundred Years of Research, Diagnosis, and Treatment	The complex disease is due to a deficiency of the lysosomal hydrolase Iduronate 2-sulfatase, which is a crucial enzyme in the gradual degradation of Heparan and dermatan sulfate.	A deficiency of Iduronate 2-sulfatase will cause damage to most tissues, organs, and systems.

10	Juan L, Jacobo C, Edwin R, Carlos J. 2019	Advances in the Development of Drug Companions for Mucopolysaccharidosis	The use of small molecules, called pharmacological chaperones (CPs), can restore the folding, trafficking, and biological activity of mutated enzymes. PCs have the advantages of wide tissue distribution, possible oral administration, lower production cost, and fewer immunogenicity issues than replacement therapy enzymatic.	CPs can increase the enzymatic activity of mutant proteins in a dependent manner, and thus decrease the symptoms of the disease.
11	Edina Poleto, Natalia G. 2020	Edition of the genome for mucopolysaccharidosis	Most MPS are inherited as autosomal recessive disorders, except for MPSII, which is X-linked. There are alternatives for the reduction of complications, one of these is gene therapy administered to patients using proteins that bind to specific segments of DNA.	Genome editing ensures that modifications are diminished, with no risk of dilution with organ growth.

12	Jorge S, Pedro G. 2018	An early case of hunter syndrome (hunter-hurler-pfaundler syndrome (mucopolysaccharidosis I dysostosis multiplex)	As a genetic disease, Hunter syndrome is determined by a mutation on the X chromosome, which affects the normal function of the enzyme Iduronate sulfatase, essential for the fragmentation of two mucopolysaccharides,	MPS is a genetic disease due to the accumulation of mucopolysaccharides, due to the lack of fragmentation of iduronate sulfatase, having more involvement in males.
			dermatansulfate and heratansulfate causing accumulation Cytoplasmic of mucopolysaccharides. It is transmitted by autosomal recessive sex-linked inheritance and is seen in males. Mucopolysaccharidosis is classified into five types of enzyme deficiency submission: Hunler, Hunter, Scheie, Sanfilippo and Morquio.	
13	KAREN ESTELA ANDRADE AVILA. 2021	STOMATOLOGICAL MANIFESTATIONS IN PATIENTS DIAGNOSED WITH MUCOPOLYSACCHARIDOSIS, A REVISIO N	Mucopolysaccharidosis (MPS) belongs to a group of inherited genetic disorders. These diseases lead to the accumulation of glycosaminoglycans in the lysosomes of most cells, the induction of progressive cell damage and multiple organ failure, resulting in the reduction of glycosaminoglycans.	The accumulation of glycosaminoglycans in lysosomes causes the induction of progressive cell damage and multiple organ failure.

		BIBLIOGRAPHIC	in life expectancy.	
14	Lindemgleccia P, William A. 2019	MUCOPOLYSACCHARIDOSE: A DOENÇA And SUAS ALTERAÇÕES ODONTOLÓGICAS	Mucopolysaccharidosis (MPS) is a genetic disease caused by an enzymatic disorder of lysosomes in the body. Wearers mainly present alterations in the number and anatomy of the teeth temporary and permanent dental problems, have a	There are alterations in number, anatomy of the temporary and permanent teeth, delayed eruption, malocclusion, macroglossia, narrow and deep palate, limitations of

			delayed eruption of permanent teeth, malocclusion (acting as a predisposing factor for caries disease), tongue protrusion, macroglossia, narrow and deep palate, limitations in opening the oral cavity, enamel defects in temporary and permanent teeth, diastemas, bruxism, caries lesions, and gingival hypertrophy.	opening of the oral cavity, enamel defects.
15	BRENA M. 2020	MUCOPOLYSACCHARIDOSIS: oral changes and the importance of dentistry in the multiprofessional care team	Mucopolysaccharidosis (MPS) represents a group of genetic diseases. Lysosomal origin, which are caused by the deficiency of enzymes that are responsible for a step in the degradation of glycosaminoglycans (GAGs). The progressive accumulation of glycosaminoglycans in Organs and tissues cause functional disorders and structural in the individual.	The progressive accumulation of glycosaminoglycans in Organs and tissues cause functional and structural disorders in the individual.
16	Rafaela T, Andrea P.	Oral and craniofacial	Hunter syndrome (also known as mucopolysaccharidosis II [MPS II]) is a disorder	Disturbed caused by poor activity of Iduronate-2-sulfatase

	2018	manifestations in to Hunter syndrome patient with	rare metabolic disease with an estimated incidence of 1	(I2S), What Has how function the
		hematopoietic STEM cell transplantation: A case report	per 100,000 live births. The disease is caused by deficient activity of iduronate-2-sulfatase (I2S), a lysosomal hydrolase responsible for the breakdown of glycosaminoglycans (GAGs). There are two ways to MPS II according to survival time and presence or absence of central nervous system involvement.	degradation of glycosaminoglycans (GAGs).
17	Sara P, Benedita M, Cristina A. 2018	Oral manifestations in children with mucopolysaccharidosis	Mucopolysaccharidosis (MPS) is a heterogeneous group of genetic disorders that occur in the oral cavity, face, and skeleton, among others. Other systems	It can be presented in the oral cavity, face, and skeleton, among other systems

18	ANTONI A R. 2020	ORAL REPERCUSSIONS OF MUCOPOLYSACCHARIDOSIS IN PEDIATRIC PATIENTS	MPS is a group of rare genetic disorders with very low prevalence. Deficiencies of specific lysosomal enzymes occur, causing GAG to accumulate in connective tissue, resulting in different degrees of multi-organ dysfunction, so preventive procedures are needed to prevent development of the disease.	It is important to keep in mind that, after the diagnosis of MPS, treatments must be carried out to achieve a better quality of life for the patient.
19	Sandra V, Louis To Angel D. 2021	Clinical and Genetic Diagnosis Mucolipidosis II - Inclusion Cell Disease	Mucolipidosis type II is a progressive debilitating pathology, with reduced musculoskeletal growth and obstruction in development after the first two years of life, in this way, psychomotor development is slow, a large percentage of these patients are unable to walk properly independent.	Due to the various complications involved in the diagnosis of MPS, the patient will present psychomotor retardation, causing difficulty in walking.

20	Rafaela Q. 2019	BUCCAL CONDITIONS AND SALIVARY METABOLITES OF PATIENTS WITH MUCOPOLYSACCHARIDE	Mucopolysaccharidosis (MPS) is an inherited genetic disease caused by a deficiency of lysosomal enzymes that affect the catabolism of glycosaminoglycans, causing their accumulation in different organs and tissues causing systemic and oral alterations	The accumulation of glycosaminoglycans in the tissues will cause specific alterations at the oral level.
21	Carmen H, Nicole M. 2021	Mandibular condyle morphology among patients with Mucopolysaccharidosis: An observational study of panoramic radiographs	Mucopolysaccharidosis (MPS) is a group of rare multisystem disorders caused by a deficiency of lysosomal enzymes necessary for the degradation of glycosaminoglycans. The accumulation of glycosaminoglycans in	The accumulation of glycosaminoglycans in organs and tissues causes neurological, cardiovascular and skeletal alterations.

			Organs and tissues cause neurological, cardiovascular and skeletal alterations, such as short stature, skeletal dysplasia, delayed motor development, limited joint mobility heart problems, respiratory failure, hepatosplenomegaly, hernias, macrocephaly, and mental retardation.	
22	Till K, Anja K. Reinhard F. 2018	Differences in maxillomandibular morphology among patients with mucopolysaccharidoses I, II, III, IV and VI: a retrospective MRI Study	Mucopolysaccharidosis (MPS) is a group of seven inherited lysosomal storage disorders caused by deficiency of 11 different lysosomal enzymes	It is an inherited disorder caused by the deficiency of 11 different lysosomal enzymes.
23	Chiel B, Emma D. 2022	Orofacial abnormalities in mucopolysaccharidosis and mucolipidosis type II and III: A systematic review	MPS, ML II, and III are rare lysosomal storage disorders. In MPS, ML II, and III, the accumulation of glycosaminoglycans (GAGs) in the lysosomes of connective tissue, connective tissue, cartilage, bone, ligaments, and other tissues. Cellular dysfunction, which ultimately leads to tissue damage and organ dysfunction. This	The accumulation of GAG in different types of tissues can cause cellular dysfunction and subsequent organ dysfunction, causing the different systemic pathologies of MPS.

			leads to multisystem changes ranging from skeletal abnormalities (so-called multiplex dysostosis), cardiorespiratory diseases, and Progressive neurocognitive dysfunction.	
24	Otal Matthew V; Cahuana Cardenas A	Manifestations Oral in Hunter Syndrome (MPS II)	Mucopolysaccharidosis is characterized by the existence of an alteration in their metabolism, caused by a deficiency of some of the lysosomal acid hydrolases that intervene in it and that leads to its intracellular storage, its elimination in the urine and a fairly uniform clinical and skeletal phenotype: dwarfism, skeletal deformities, joint stiffness, abdominal hernias, deafness, cataracts, hepatosplenomegaly, cardiac involvement, mental retardation and alterations in the stomatognathic area, patients with this syndrome tend to have preserved muscle strength and tone, diastemas, macroglossia, delayed tooth eruption and small, flattened condyles	MPS syndrome tend to have preserved muscle strength and tone, diastemas, macroglossia, delayed tooth eruption, and small, flattened condyles.

25	Michal Straka; Lubos danisovic; Vladimir Bzduch	The significance of electron microscopic examination of gingiva in cases of Hunter syndrome and hereditary gingival fibromatosis	Hunter syndrome belongs to the group of diseases Hereditary Idiopathic gingival hyperplasia is a rare inherited condition that affects one in 750,000 people and can occur in both sexes and in either jaw, characterized by fibrous enlargement, Non-hemorrhagic and slowly progressive maxillary and mandibular keratinized gum caused by increased elements of mucosal connective tissue.	Patients with hunter syndrome may present with idiopathic gingival hyperplasia, characterized by a fibrous, non-hemorrhagic and slowly progressive enlargement of the maxillary and mandibular keratinized gums due to the increase of connective tissue of the mucosa.

Note.

Source: Ponce Reyes Nathalie, 2023

D'avanzo (6) and Chuang CK (1) claim that mucopolysaccharidosis type II, also known as Hunter syndrome, is a rare genetic alteration, which is generated by inheritance due to defective chromosomal traits of the parents, and there are seven main types of MPS: MPS I, II, III, IV, VI, VII and IX. This syndrome presents dysfunction of the organ-systems, which will prominently include the brain in most patients, causing a severe clinical phenotype.

In addition, Pérez-López (7) and Bode CJ, Dogterom (2) mention that MPS II is a rare disease with a prevalence at birth of 1.3 cases per 100,000 male births. Since it is X-linked, males are almost exclusively affected, although there have been cases of heterozygous females showing signs or symptoms and some homozygous cases and there is a great deal of variety in the way the disorder presents

According to Semyachkina (8) and Cáceres (9), this syndrome is also characterized by short stature, changes in facial features such as gargoylemism, skeletal anomalies, cardiac pathologies, airway obstruction (obstructive sleep apnea), umbilical hernia, conductive deafness, among others. This is a progressive debilitating pathology, with reduced musculoskeletal growth and obstruction in development after the first two years of life. In this way, psychomotor development is slow, a large percentage of these patients are unable to walk independently, Semyachkina AN (8) says that there will be two types of phenotypes, the most severe will appear between 18 months and 4 years after the clinical manifestations, while the milder will generally manifest from the age of 60 onwards these will have normal intelligence and longer life expectancy, the progression of symptoms is variable, it is for this reason that the diagnosis cannot be made immediately and Díaz JCL (10) with Campano mdlcc (11) mention that, in most cases, patients in their second decade of life usually die from heart and respiratory failure, in the most severe cases. while in mild cases life expectancy is somewhat higher

Mota BC (12) says that some general clinical manifestations are: joint stiffness, short stature, hearing loss, respiratory anomalies, macrocephaly, heart disease, distended abdomen. It is one of the groups of MPS with the greatest developmental delay and presents difficulty in flexing the fingers and motor coordination deficits

Cáceres Matta (13) and Torres R (15) say that the craniofacial features in this syndrome are similar to those of Hurler syndrome (MPS type I). The head is enlarged, with a prominent forehead, often the supraorbital area; Marked temporal ridges and protrusions, rhinitis with rhinorrhea, endocranial hypertension, heart disease such as thickening of the heart valve, aortic stenosis, heart failure, arrhythmias and corneal opacity are common in these patients. respiratory infections or heart complications.

Andrea Vaz (16) and Anneliese L (17) Both authors agree that Hunter syndrome, or mucopolysaccharidosis II (MPS II), is a rare metabolic disorder caused by deficiency of the enzyme iduronate-2-sulfatase (I2S), resulting in abnormal accumulation of glycosaminoglycans (GAGs) and multiple organ dysfunction. Both acknowledge that the clinical manifestations of MPS II vary in terms of age of onset, disease progression, and severity of symptoms. In addition, both describe oral and craniofacial features common in patients with MPS II, such as macroglossia, open bite, diastemas, and periodontal problems. They also highlight the importance of a comprehensive management approach that includes multidisciplinary clinical support and targeted therapies.

Amira Abdelhefeez (18), Scott D. Groose (19) and Andrea P (20) talk about how Hunter syndrome (HS) is a serious metabolic disorder with heterogeneous multisystem manifestations, including oral problems, oral problems, and oral health. During the first year of follow-up, a significant improvement in their oral health-related quality of life was observed.

Sara P (21) and Rafaela T (22) mention that these patients have a higher prevalence of dental problems, such as delayed tooth eruption, alterations in dental morphology, occlusal problems, dental caries and bleeding gums. This highlights the need to improve diagnostic and prevention protocols to improve the oral health of these patients and promote efficient oral care strategies with parents/caregivers.

Otal Mateo (23) and Francesca D' (24) say that in Hunter syndrome, a rare genetic disease known as mucopolysaccharidosis type II, various clinical manifestations can be observed, including delayed dental development, malocclusion, gingivitis and periodontal disease, macroglossia, alterations in tooth enamel, in addition to systemic manifestations in other systems of the body. These oral manifestations, which vary in severity and presentation, can affect tooth alignment, gum health, speech function, and swallowing, and require regular, personalized dental care in collaboration with health care professionals to comprehensively address all clinical needs associated with Hunter and Michal Straka syndrome (25) Transmission electron microscopy is a valuable tool in the study of diseases affecting the gums, as it provides a detailed view of the cellular structure and extracellular matrix, helping to understand the pathological mechanisms and evaluate the efficacy of treatments and to identify the manifestations that occurred.

Conclusion

According to the study carried out, the information describes that it is a recessive disease linked to the X chromosome, men are more likely to develop the syndrome, the deficiency of the enzyme iduronate2 sulfatase thus triggering the characteristics of this, therefore, the findings through the research helped concretely to establish the presumptive diagnosis because the characteristics of the patient coincide with the respective information that highlights the syndrome, That is, in the dental area, there are distinctive features in the facial massif and in the dental anatomy.

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Author Details

Ponce Reyes, Nathalie SteffyI; Grijalva Palacios, Miryan Margarita II; Luis Fernando Andrade Andrade III; Chandi Chauca Kevin Alexander IV.

I ui.nathaliepr73@uniandes.edu.ec, Professor, Universidad Regional Autónoma de Los Andes UNIANDES, https://orcid.org/0000-0002-1396-1236, Ibarra-Ecuador.

II ui.miryangp00@uniandes.edu.ec, Professor, Universidad Regional Autónoma de Los Andes UNIANDES, https://orcid.org/0000-0002-6808-279X, Ibarra-Ecuador.

III luisfaa92@uniandes.edu.ec, Student, Universidad Regional Autónoma de Los Andes UNIANDES, https://orcid.org/0000-0001-5876-866X, Ibarra-Ecuador.

IV kevincc19@uniandes.edu.ec, Student, Universidad Regional Autónoma de Los Andes UNIANDES, https://orcid.org/0000-0001-8028-758X, Ibarra-Ecuador.