Universidad Europea

TRABAJO DE FIN DE GRADO

Grado en Odontología

GENETIC PREDISPOSITION FOR DEVELOPING ORAL PATHOLOGIES AS INDICATOR FOR UNDERLYING ASSOCIATED PATHOLOGIES

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Summary in Spanish

Introducción: El ADN contiene toda la información genética que define todos los aspectos de nuestro cuerpo y nuestra mente. Definen todos los aspectos de nuestro cuerpo y nuestra mente. Por desgracia, las mutaciones pueden dar lugar a enfermedades genéticas que afectan a la salud oral y sistémica de una persona. Muchas de las enfermedades se definen como enfermedades genéticas raras, lo que conlleva dificultades en cuanto a un diagnóstico adecuado y seguro, causando la necesidad de que los dentistas y los médicos se informen sobre las enfermedades genéticas raras, demandando una colaboración interdisciplinar para poder tratar al paciente lo mejor posible.

Metodología: Se ha realizado una investigación sistémica que incluye 28 artículos y 3 libros, publicados en inglés y alemán y que proporcionan una profunda información sobre los signos y síntomas de patologías orales tempranas que se asocian a enfermedades genéticas sistémicas subyacentes.

Discusión: El conocimiento de estas enfermedades, sus manifestaciones y causas, da al dentista la posibilidad de establecer un diagnóstico precoz, para inducir los pasos siguientes de diagnóstico y tratamiento del paciente. Cuando los pacientes con enfermedades genéticas raras tienen la oportunidad de ser diagnosticados adecuadamente por el sistema sanitario, se crea una base para la prevención. Además, gracias al rápido avance de las ciencias y las técnicas de gran potencial, existe la posibilidad de prevenir las enfermedades genéticas raras en el futuro.

Conclusión: Los profesionales sanitarios deben continuar e intensificar su educación sobre las enfermedades genéticas raras. Además, es necesario realizar más investigaciones para obtener un conocimiento más profundo y una cantidad suficiente de datos sobre las enfermedades genéticas raras para facilitar un diagnóstico temprano y correcto.

Abstract

Introduction: DNA contains all the genetic information that defines every single aspect of our bodies and minds. Unfortunately, can mutations lead to genetic diseases affecting the oral and systemic health of a human being. Many of the diseases are defined as rare genetic diseases, leading to difficulties regarding a proper and certain diagnosis, causing the necessity of dentists and practitioners to train themselves regarding the manifestation and causes of rare genetic diseases, demanding an interdisciplinary collaboration in order to give the best possible care the patient.

Methodology: A systemic research was conducted including 28 articles and 3 books, published in English and German and providing profound information about signs and symptoms of oral pathologies that are associated with underlying genetic systemic diseases.

Results: The following genetic systemic diseases were studied that all present an early onset of oral pathologies like Hereditary Hemorrhagic Telangiectasia, Peutz-Jeghers Syndrome**,** Pseudoxanthoma Elasticum, White Sponge Nevus, and Basal Cell Nevus Syndrome.

Discussion: The knowledge about these diseases, their manifestations, and causes, gives the dentist the possibility to establish an early diagnosis, for inducing further steps of diagnosis and treatment of the patient. When patients with rare genetic diseases get the chance to be properly diagnosed by the health care system, is a foundation for prevention created. Additionally, because of the fast advancement of sciences and promising techniques, there is hope for the prevention of rare genetic diseases in the future.

Conclusion: Health care professionals need to continue and intensify their education about rare genetic diseases. Furthermore, more research needs to be undertaken to

collect more profound knowledge and a sufficient quantity of data about rare genetic diseases to facilitate an early and correct diagnosis.

Index

1. Introduction

Every aspect of a human being is determined by a certain sequence of chemical bases forming an extremely large organic molecule in form of a double helix, hidden in the cell nucleolus of every cell: The deoxyribonucleic acid, also called DNA. The human DNA presents the inherited genetic material, being composed of a backbone made of a pentose sugar and a phosphate group and a certain combination of nitrogenous bases of adenine, guanine, thymine, and cytosine [(1)]. The DNA Helix is coiled up to the shape of chromosomes, forming the human genome.

The human genome itself is composed of 23 chromosome pairs, 22 of them are autosomal chromosomes, whereas one pair of them is determining the sex of the individual (see Figure 1). The genes are unevenly distributed over the chromosomes, forming areas of gene-rich sections and others of gene-poor sections [(2)], meaning that some DNA sequences encode the synthesis of either RNA or a protein and others do not, providing a total amount of information of 4 megabytes [(3)].

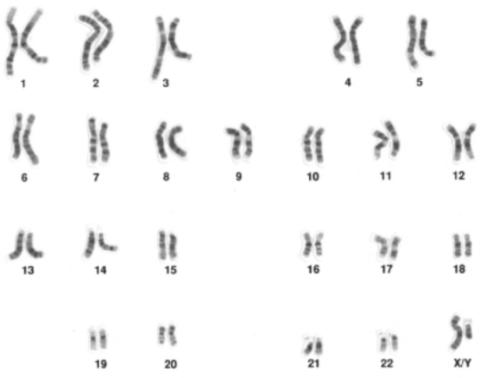

Fig. 1. Human Genome composed of 23 chromosome pairs (2)

With the individual sequencing of the chemical base pairs that the DNA is composed of, the genome is individual for every person, determining the individual aspects and characteristics of a human being, including if an individual suffers a genetic disease or how an individual will react to a certain treatment [(2)].

A genetic disorder can be caused by multiple conditions, usually by an aberration of a gene or chromosome [(2)]. It can be caused by an absence of a chromosome or the existence of an additional one, a mutation, or even only a simple variation of one gene.

This can lead to either the full expression of a disease or simply to a predisposition for a disease, that only will manifest in combination with certain environmental factors [2]. Even though sometimes multiple genes can be responsible for causing a disease, so far 2.200 diseases were discovered, where the disease-causing gene was identified [2]. It is a fast advancing scientific area that is further examined and that discovers with every day more and more connections between genetic changes and its caused diseases and that already in the past achieved big accomplishments [3]. One of the most important advancements lately, has been the human genome project, which was completed in the year 2003. With the help of international efforts, 3.1 billion DNA base pairs were analyzed and in total between 20.000 and 25.000 genes were found [4], completing a full determination of the complete human genome.

This created a new base for the biomedical sciences and created a ground for numerous new developments [3]. Applied to the medical area it helped to explore diseases on a deeper level, meaning on a cellular level [3]. This leads to a deeper understanding of genetic predispositions for a disease and its development [2][3], presenting new opportunities for diagnostic methods and treatment possibilities, avoiding unnecessary invasive diagnostic interventions and giving the opportunity of improved methods for prevention, and treatment possibilities [2].

Using these advances in Sciences, especially in the area of diagnostics, the possibility of genetic testing improved a lot. Genetic testing allows us to examine the DNA isolated from body fluid samples from different individuals, providing us with information about the human genome, indicating if the examined individual suffers from a genetic disease or predisposition for a disease. So far there were seven different types of genetic tests developed. There is the carrier testing to see if a person carries a copy of a gene that could cause a genetic disorder in a child, the prenatal testing which looks for changes

in the genetic material of a fetus, the newborn screening that is done in newly born children to see if they suffer a genetic disorder to be able to treat it in a timely manner, the predictive testing that is done in adults to validate to the probability of the onset of a disorder, the diagnostic testing to specifically confirm or exclude a certain genetic condition, the forensic testing that is applied in the field of forensics for the identification of victims and the research testing that is used to further research the genetics to find new genes and to investigate new genetic diseases [5].

All types of genetic tests facilitate the diagnosis of a disease and its treatment, even if the test result is negative, it narrows down the range of possible diagnoses. This provides not only health care professionals in general with new possibilities but also does it provide the dental profession with a whole new perspective.

The dentist as a health care professional has an obligation to care not only for the oral health but also for the general health of a patient. Dentistry as a discipline cannot be separated from the discipline of medicine. The oral cavity and adjacent tissues are embedded in the system of the body and with that, they have a mutual influence on each other. The best evidence of this is the well-proven relationship between oral health and the effect on very prevalent systemic diseases like cardiovascular diseases, diabetes, cancers, and lung diseases within the population [6]. To provide the best medical care possible, there needs to be an interdisciplinary collaboration. This is because dental treatments can have a severe systemic effect and medical conditions can have a big influence on dental treatments. Many systemic diseases express oral symptoms or even precede systemic diseases, the dentist must pay attention to them during routine check-ups and treatments. Since the last two decades, the awareness has been raised about this connection and the knowledge about this aspect is rapidly progressing [2]. Therefore it is worthy to highlight the importance of dentists to train

themselves about the latest developments and new scientific findings, as well as to educate the patients about the importance of oral health and its effects on the whole body. Demanding of physicians to do the same to be able to work together with the dentist in a properly and productively way, for the health care system to provide the best integral care possible [2].

Dentistry in combination with genetic testing and specializations on oral pathologies that can indicate a systemic pathology, a dentist can be crucial for indicating which patients should be genetically investigated [6], offering a whole new level of prevention, early diagnosis, and improved treatment options.

2. Objectives

This work aims to investigate and discuss the following objectives:

Primary objectives:

1. Study of genetic systemic diseases that present an early onset of oral signs and symptoms, their origin, development, and presentation.

Secondary objectives:

1. Assessment if oral pathologies of genetic systemic diseases can be used to facilitate the diagnosis of the underlying associated pathology/disease.
2. Assessment if oral pathologies of genetic systemic diseases can be used for prevention of the underlying associated pathology/disease.

3. Methodology

This article aims to systematically study the topic of oral pathologies that can indicate underlying systemic diseases with a genetic predisposition. Therefore, the selection criteria for scientific articles and journals were based on covering the named topic. Furthermore, only articles written in English and German, published after 2011 were included, to provide the most recent information. Two books published in the years 2009 and 2017 were included because they provide fundamental knowledge about basic principles about genetics and rare genetic diseases.

The search methodology is based on a full access connection for UEM students, using a specific UEM library page “descubre.uem.es”, covering databases MEDLINE Complete, Academic Search Ultimate, Complementary Index, Scopus, and Scientific Citation Index. Additional databases of PubMed, MedLine, and Google scholar were searched.

All found articles were carefully considered after evaluating the Abstract and reading the article. 28 Articles were included after careful consideration and 3 books, providing information about genetics, oral pathologies, and systemic diseases.

Exclusion criteria were if exclusively information was provided about oral diseases connected to a systemic disease, but non-genetic based. A flow diagram was designed presenting the search strategy and screening process (see Figure 2).

Keywords: Genetic predisposition for oral and systemic pathologies; Oral pathologies and systemic diseases; Genetic testing; Human genome project; Hereditary Hemorrhagic Telangiectasia; Peutz-Jeghers Syndrome**;** Pseudoxanthoma Elasticum; White Sponge Nevus; Basal Cell Nevus Syndrome; Prevention genetic diseases;

Inclusion criteria:

- Case reports, cohort and case-control studies, pilot studies
- Published between 2011-2021
- Articles in English and German
- Studying of genetic diseases that express oral signs and symptoms
- Fundamental information about DNA and human genetics
- Genetic testing for genetic diseases
- Treatment possibilities for genetic diseases
- Genetic diseases that express early oral diseases
- Genetic diseases with a possibility of an early diagnosis by the dentist

Exclusion criteria:

- Subjective questionnaires, expert opinions
- Genetic systemic diseases without relation to oral symptoms
- Genetic systemic diseases with late oral signs and symptoms

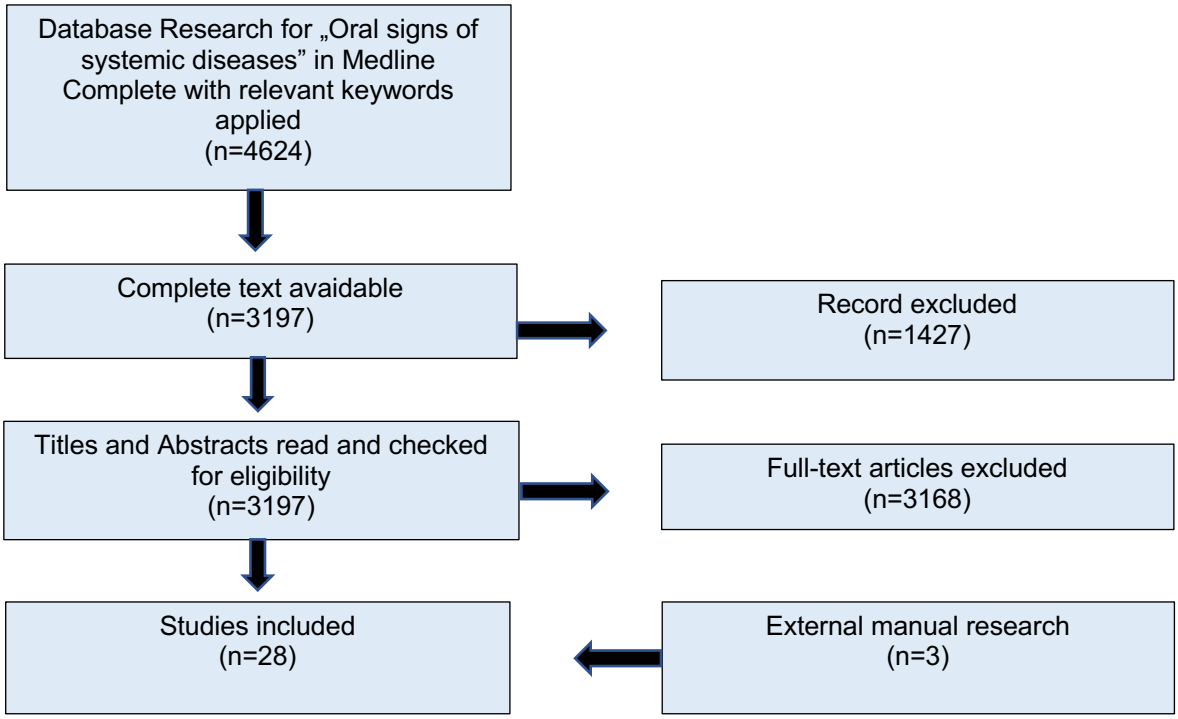

Figure 2 Search strategy and screening process

4. Results

4.1. Study of genetic systemic diseases that present an early onset of oral signs and symptoms, their origin, development, and presentation.

4.1.1. Hereditary Hemorrhagic Telangiectasia

The disease Hereditary Hemorrhagic Telangiectasia (HHT), also called Osler-Weber-Rendu disease (OWRD) [7–11], is an autosomal dominant disease [7–9,11,12], with a prevalence of about 1: 10 000 [11,12]. Five different subtypes of the disease were identified, whereas type 1 and 2 are the most prevalent ones [10]. The different types of HHT are defined by the gene that mutated. Type 1 is produced by the mutation of the endoglin gene on chromosome 9q34.1 and Type 2 by the mutation of the activin receptor gene on chromosome 12q1 [7,10,12]. Type 3 and 4 are mapped on chromosomes 5 and 7, whereas the fifth type is caused by a mutation on the GDF2 gene on chromosome 10q11 [7]. The disease is based on, a by the mutation caused defective production of proteins that are fundamental for the endothelial wall integrity [10], leading to arteriovenous malformations [7] with an overall affection of the organism, with the consequence of multiple possible complications in the lungs, liver, intestines, spinal cord and brain [10]. A broad range of possible occurring pathologies can be caused like high-flow arteriovenous fistulae in the brain and spinal cord, capillary telangiectasia, cerebral ischemia and abscesses caused by pulmonary vascular shunts, and cerebrovascular malformations [12]. The frequency of occurrence of the manifestations of the disease

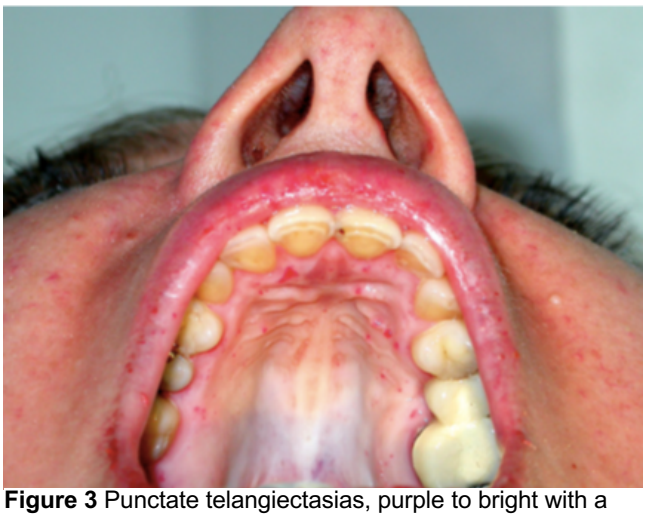

Figure 3 Punctate telangiectasias, purple to bright with a spiderlike appearance and located in the area of the palate (11)

increase with age [7], meaning that patients at a young age most likely do not express all signs and symptoms of the diseases yet [12]. The majority develop recurrent episodes of epistaxis during childhood or later in adolescence [8], 90% of the patients have it before they reach the age of 20 [13]. Later in childhood usually Punctate telangiectasis appears on lips, tongue, fingers, and the overall skin. Arterial malformations of the brain, lung, and liver can occur at any age but are more prone to cause bleedings and further complications at a mid-adult age and later on [8]. The Diagnosis of the genetic disease is primarily clinical and based on Curaçao's diagnostic criteria, defined in the year 1997, defining four signs that must be present to diagnose the disease [9]. They are recurrent epistaxis, cutaneous mucosal telangiectasia, a family history of the disease, and visceral arteriovenous malformations in the lungs, the liver, brain, or in the intestines [8–10,13]. The diagnosis is considered definite, when the patient presents three or more of the criteria, is suspected when there are two of the criteria fulfilled, and unlikely when there are less than two criteria present [10,11]. The diagnosis can be confirmed by a molecular genetic test [13].

Oral lesions that are most commonly already developed during childhood, are punctate telangiectasias on the tongue and lips and present a punctuate, spider-like, or nodular appearance, and they are located in the area of the tongue, lips, palate, and gingivae. In color, they vary from purple to bright red (see Figure 3). There is also the possibility of finding oral vascular malformations, hemorrhagic vesicles, and ulcers on the mucosa and gingivae [7]. Because of this Etiopathogenesis, the dentist must be aware of the increased risk of bleeding [9,10] and increased risk of infection.

4.1.2. Peutz-Jeghers Syndrome

The Peutz-Jeghers Syndrome PJS is an autosomal dominant inherited disease [7,14–18] with a prevalence of 12 - 30.000 [18]. The Male-to-female ratio is 1:1 [18]. It is caused by the mutation of the gene STK11 on chromosome 19 [7,14–18]. It is a tumor suppressor gene [14] involved in the regulation of metabolism, cell growth, and cell polarity [16].

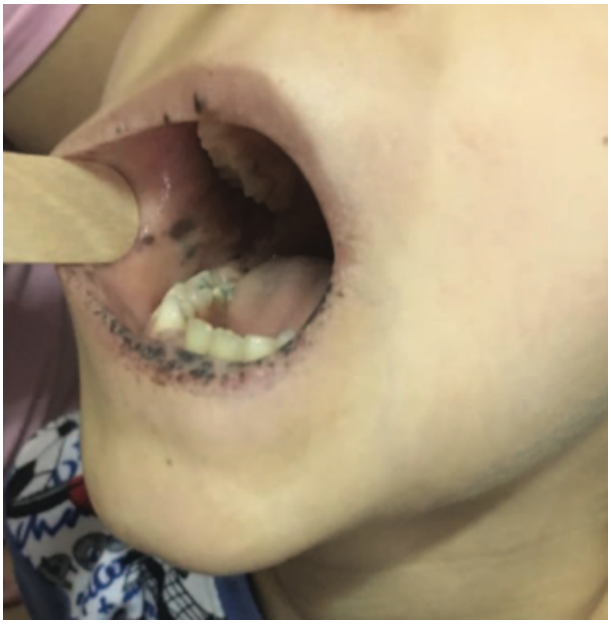

Figure 4 Mucocutaneous hyperpigmentation with a color of dark brown to black in shape of round and oval pigmentation irregular distributed over lips and buccal mucosa (17)

Since the mutation can be variable in the phenotype the manifestation that can be seen are variable as well, in sense of different presentations of the macules, location of the polyps, and development of different types of cancer [14].

The disease is mainly expressed by the clinical manifestations of oral mucocutaneous hyperpigmentation [7,14–18] that is present in 95% of all patients [17] (see Figure 4). They have the form of round, oval or irregular pigmented areas with a diameter of 1-1,5 mm with a color of dark brown to black and are irregularly distributed throughout the oral mucosa [14]. A malignant development of the lesions is not to be expected and possibly disappears during adolescence [17]. Whereas the polyps grow with time, causing later on in life complications like abdominal pain, gastrointestinal bleeding, intestinal obstructions [14,16], loss of appetite, and associated weight loss [14]. The bleedings can cause chronic anemia, leading to fatigue and dizziness [14]. They are most commonly located in the small colon and the bowl with a likelihood of 64%, followed by the stomach with 49% and the rectum with 32% [17]. The mucocutaneous manifestations are most prominent at a young age and are fading with time [14,17]. They are mainly

present on the lips and oral mucosa but can be also present on the hands and feet or even in the periorbital, perianal and genital area [17]. In the case that a patient is already in an advanced stage of the disease, Angular cheilitis is common to be found, because of anemia that is caused by disease-induced intestinal bleedings [17]. Additionally, is the risk for developing cancer significantly higher than in healthy patients.

The classic criteria for the diagnosis are a positive family history, the presence of the characteristic mucocutaneous pigmentation, and a histopathological examination of a by the disease caused polyps [14,15].

Since the disease presents a high potential for severe gastrointestinal complications and malignant changes an early diagnosis can be essential [16,17]. Especially patients of an advanced age who most likely already developed polyps and malignant changes [17], a rapid diagnosis should not be delayed, in order to prevent any further complications.

4.1.3. Pseudoxanthoma Elasticum

The disease Pseudoxanthoma Elasticum (PXE), also called Grönblad-Strandberg syndrome [19], is a disease that is autosomal recessive inherited [19,20] and occurs with a prevalence of 1:25 000 to 1:100 000 [19–21], having a higher prevlanece in women over men, 2:1 [20,21]. A mutation of the gene ABCC6 is the root cause of this disease. The mechanism of the disease is not fully clear yet, since the gene ABCC6 encodes for an ATP-dependent transmembrane transporter, which can be found mainly in the kidneys and the liver [20]. Different mechanisms of how the disease may affect the body are suggested, there is the possibility of insufficient secretion of inhibitors leading to an abnormal calcification of tissues [20] or a diminished or even non-existent transmembrane transport of extracellular material leading to its accumulation inside of

the cell [21]. However the exact mechanism of the disease might be, does the mutation of the ABCC6 gene lead to calcifications of elastic fibers and subsequently to fragmentation of them [19,21,22]. This leads to a degenerative alteration of all tissues that are rich in elastic fibers [19] resulting in a broad affection of all kinds of organ systems. This is the reason why in literature the disease is described as a multisystemic disease [20] or multi-targeted disorder [19,22] because of the multiple possibilities of manifestation of the disease [19–22].

Commonly affected are skin, eyes, and the cardiovascular systems. The skin can present multiple small yellow papules [19,20,22], and due to its laxity, they are especially present in the area of the neck, groin, armpits, and flexural area of arms and legs [19,22]. In the eyes, several manifestations can be noticed like angioid streaks, which are pigmented lines spreading from the optic disc [22], hemorrhages [19,22], and loss of vision [20]. Cardiovascular manifestations are expressed in multiples ways, including angina pectoris, a decreased peripheral pulse, and high blood pressure [19,22]. The broad affection of the organ systems leads to significant morbidity and infrequently also to mortality [20].

Oral symptoms are most commonly to find in the lower and upper lip, followed by the floor of the mouth, the hard palate, and the gums [19,21]. The manifestation show yellowish-white papules, macules, or patches with a reticular growth pattern [7,19–21] (see Figure 5). In the case of a biopsy, the histopathological findings of the oral lesions show the calcified and subsequently fragmented elastic fibers alongside healthy connective tissue, using the Kossa staining

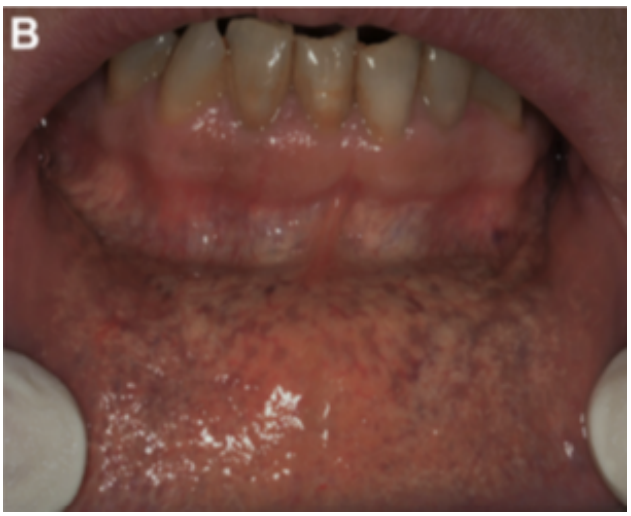

Figure 5. Multiple yellowish papules of the lower lip (22)

to reveal the calcium deposits and the Orcein to show the destroyed structure of the elastic fibers [20,22].

Further described manifestations that can be found by the dentist are described as dental developmental abnormalities like oligodontia and amelogenesis imperfecta as well as temporomandibular changes [19].

The broad affection of multiple organs including big differences in extension, onset, and involvement of the organs [20], makes the diagnosis of this disease very difficult [19,21,22] or leaves it in many cases undiagnosed [21]. This highlights the necessity of interdisciplinary cooperation of dermatologists, cardiologists, dentists, pathologists, and ophthalmologists to establish a proper and accurate diagnosis [22].

In the year 1992 diagnostic criteria were at the consensus meeting established. It includes major and minor criteria. Major criteria include characteristic skin lesions, a typical histopathological finding of lesioned skin, and an ocular lesion in patients older than 20 years old. Minor criteria are histopathological findings of non-lesional skin and a first-degree relative diseased with PXE [22].

A useful method for diagnosis that is also included in the diagnostic criteria of 1992 is the biopsy with a histopathological exploration of the sample [20], there are cases though where cutaneous findings are not present or where a biopsy of the skin fails to prove the for the disease characteristic histopathological findings [19,21]. In these cases can a biopsy of the oral mucosa lead to a clear and final diagnosis of the disease [22], especially because oral lesions might appear even before the cutaneous lesions [21].

Early detection of the disease is fundamental because of its multisystemic character, to prevent as good as possible morbidity and mortality, with the help of a proper follow-up and the best possible treatments [21].

4.1.4. White sponge nevus

White sponge nevus is an autosomal dominant inherited disease [23–25] with no gender tendency [23]. The prevalence is precisely known but is estimated to be around 1:200 000 [7,24]. It is caused by the mutation of the gene cytokeratin 3 and 13 [7,23–25]. The cytokeratin refer to more than 20 proteins that are part of the cytoskeleton of epithelial cells that are present in the non-keratinized oral mucosa [7,24], nasal, oesophageal, and anogenital epithelia, causing weakened stability of keratin and tonofilament aggregation, causing an instability of the cells [23]. The disease has a very unsteady penetrance and a not consistent expressivity [24,25].

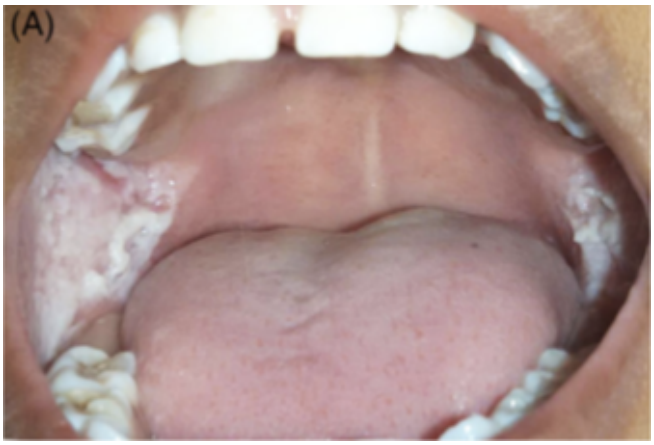

Figure 6 White, diffuse and corrugated plaques bilaterally on the buccal mucosa (23)

The manifestation of the disease is most commonly already developed during childhood [24,25] and is located in the oral, esophageal, or genial epithelia [7,23,25]. They are present as whitish or grey plaques that are thickened in structure and present a velvety and spongy texture [7,23–25] (see Figure 6). Characteristically does the lesion not disappear on stretching and can be rubbed off [24]. The whitish lesions can vary considerately in size and distribution and can even change over time [23]. They are asymptomatic [7,23,24] and are most commonly seen orally, located bilaterally in the oral cavity on the buccal mucosa, followed by the labial epithelia, the gums, and the floor of the mouth [23]. A malignant development is not to be expected, the manifestations are benign [23,24]. The main complaint of patients is the appearance of the manifestations [23].

A biopsy can be taken to rule out possibly or definitive malignant differential diagnoses [23,24] like oral leukoplakia, squamous cell carcinoma, oral lichen planus, lupus erythematous, early smokeless tobacco lesions, or secondary syphilis [23].

The sample will show microscopically a typical picture of hyperkeratosis [23,25], a perinuclear eosinophilic condensation [23,24], and epithelial thickening [23,25].

4.1.5. Basal Cell Nevus Syndrome

The disease Basal Cell Nevus Syndrome, also called Gorlin-Goltz Syndrome (GGS) [26,27], is an autosomal dominant inherited disorder with a prevalence of 1:60 000 [26,27], with a higher affection of men than women with a ratio of 3:1 [27]. It is caused by a mutation of the human patched gene PTCH1 on chromosome 9p22.3-q31, which is a tumor suppressor gene [26,27]. The effect of this mutation expresses itself in a broad range of manifestations, varying from oral lesions up to musculoskeletal malformations [26].

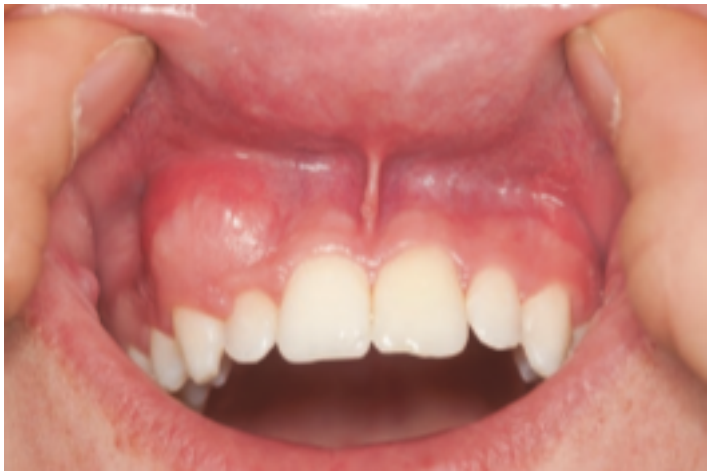

Figure 7 Odontogenic keratocyst

Often seen manifestations of the disease are multiple Basal cell carcinoma, palmar pits, intracranial ectopic calcifications of the falx cerebri, as well as neurological, ophthalmic, endocrine, and genital manifestations [26,27]. Orally can be frequently found odontogenic keratocyst in the jaw [26,27] (see Figure 7) and a broad range of malformations of the hard and soft tissues like a high-arched palate, cleft lips or palate, hypertrophy of the gums, tongue, buccal and palatal mucosa [27]. Furthermore can patients present agenesis, oligodontia, hypodontia, microdontia, dysplasia, enamel

fragility and defects, delayed eruption of teeth, irregular teeth spacing, and prognathism and malocclusion [26].

Another common and most consistent manifestation of the disease is the Keratocystic odontogenic tumor (KCOT). Multiple KCOTs with a characteristic invasive growth pattern that potentially causes destruction of the invaded tissues can be used as diagnostic criteria to support the diagnosis of disease [7,26].

In the case of a biopsy can be histopathologically seen that the KCOT in GGS presents different characteristics as a sporadic KCOT, because it presents a higher epithelial proliferation including mitosis and inflammatory infiltration, with the presence of daughter cysts which seems to explain the high rate of recurrence of this kind of tumors [26].

Because of the potentially malignant development of the disease is an early diagnosis and good genetic counseling is especially important to prevent and manage possible malignancies and maxillo-facial harm [26].

Tabel 1 Summary of the results

	Affected gene	Pathophysiology	Oral signs	Systemic signs
Hereditary Hemorrhagic Telangiectasia	**Type 1:** Endoglin gene on chromosome 9p34.1 [7,10,12] **Type 2**: Activin receptor gene on chromosome 12p1 [7,10,12] **Type3/4:** Mutation on chromosome 5 and 7 [7] **Type 5:** GDF2 on chromosome 10p11[7]	Defective production of proteins fundamental for the endothelial wall integrity casing arteriovascular malformations [7,10]	Punctate telangiectasia in tongue and lips [7,11]	• Recurrent episodes of Epistaxis [8-10,13] • High-flow arteriovenous fistulae in brain and spinal cord [12] • Capillary telangiectasia [12] • Cerebral ischemia and abscesses [12]
Peutz-Jehgers Syndrome	STK 11 on chromosome 19 [7,14-18]	Mutation of a tumor suppressor gene that is involved in the regulation of the metabolism, cell growth and cell polarity [14,16]	• Mucocutaneous hyperpigmentation [7,14-18] • Angular cheilitis [17]	• Multiple intestinal polyps [14] • Periorbital/perianal/genital hyperpigmentation [17] • Gastrointestinal bleedings [14,16] • Intestinal obstructions [14,16] • Chronic anemia [14] • Weight loss [14]
Pseudoxanthoma Elasticum	ABCC6 (7,19-21)	The exact mechanism is not known yet, but the mutation leads to calcification of elastic fibers[20] and subsequently to fragmentation of them [19,21,22]	Papules, macule or patches of yellow-white color with a reticular growth pattern [7, 19-21]. Most commonly located on lower and upper lips, followed by the floor of the mouth, hard palate and the gums [19,21].	• Multiple small yellow papules located in the area of neck, groin, armpits and flexor arms and legs [19,20,22] • Angioid streaks [22] • Loss of vision [20] • Angina pectoris [19,22] • Decreased peripheral pulse [19,22] • High blood pressure [19,22]
White sponge nevus	Cytokeratin 3 and 13 [7, 23-25]	Affection of the production of more than 20 different proteins that are part of the cytoskeleton of epithelial cells [7,24], causing a weakened stability of keratin and monofilament aggregation leading to an instability of cells [23].	Plaques of whitish or grey color, thickened in structure with a velvety and spongy structure [7, 23-25], most commonly located bilaterally in the buccal mucosa followed by the labial epithelia, gums and the floor of the mouth [23]	Plaques can be located as well esophageal or genital epithelia [7,23,25]
Basal Cell Nevus Syndrome	PTCH1 on chromosome 9p22.3 [26,27]	Mutation of a tumor suppressor gene causing a broad range of manifestations [26,27]	• Odontogenic keratocytes [26,27] • Broad range of possible malformations of hard and soft tissues like hypertrophy of the tongue, gums and mucosa [27], agenesis, oligodontia, hypodontia, microdontia, dysplasia, enamel fragility, delayed eruption, irregular teeth spacing, prognathism and malocclusion [26]	• Multiple basal cell carcinoma [26,27] • Palmar pits • Intracranial ectopic calcifications of flax cerebri [26,27]

5. Discussion

5.1. Assessment if oral pathologies of genetic systemic diseases can be used to facilitate the diagnosis of the underlying associated pathology/disease.

The human body is composed of different organ systems, which can not be seen as individual independent systems but as one big system where all parts influence each other and moreover are dependent on each other. This leads to the fact that oral and systemic health have a reciprocal relationship. They influence each other, the oral health has an effect on systemic health, and vice versa, systemic health has an effect on oral health. This actively demonstrates that it is essential that dentists have to be trained in systemic diseases of the body and their affection of oral health and that physicians have to be trained not only within their specialization but also in general about diseases of other areas, including the one of the dentists. This overall knowledge about the human body is inevitable to understand the pathogenesis of manifestations that a specialist might find in their area of specialization. They need to be able to understand if they have found the origin of the present disease or the consequent manifestations of a disease. This is necessary for professionals to be able to establish a correct diagnosis and with that to reduce the possible morbidity and mortality of a patient [21]. They can initiate the needed steps for further diagnosis or the right treatment. For dentists this means to be able to identify an oral lesion as a possible manifestation of a systemic disease, transferring the patient to the adequate practitioner for further examination and treatment. They need to be able to explain to the patient the necessity for diagnosis and the possible risks and advantages of diagnosing the suspected disease correctly. Furthermore, does the dentist need to know if a biopsy needs to be done to secure a diagnosis. Often can it be particularly

useful to look for the specific histopathological changes in the sample to support the diagnosis, especially in cases where cutaneous findings are minimal or absent [19,21].

In terms of equality of human beings and the right of everyone to health, it is an obligation of health care workers to educate themselves as well in rare diseases but especially also in inherited diseases. This is because in these cases the possibility of inheritance of the disease to descendants is given, and often a certain pattern of inheritance, like recessive or dominant inheritance, can be seen. The family history can in this case help to establish an early and reliable diagnosis.

Along this lines up that patients with rare inherited diseases have just like everybody else a right to proper diagnosis and appropriate treatment. But often they are not aware of their condition and for a long time undiagnosed, which can lead in some cases to a critical and life-threatening development of the disease. For example in the case of a patient with Basal Cell Nervus Syndrome an early diagnosis and a proper follow-up protocol is crucial to managing as good as possible the consequences of the disease, which are in this case malignancies and maxillofacial deformations and destruction [19].

Especially the dentist has a good chance to suspect and initiate a diagnosis of rare genetic diseases. This is because oral pathologies as caries and periodontal pathologies are often already present from an early age on and because they are common to find in the population, moreover they often lead to considerate discomfort and with that often a dentist is consulted. This means that the dentist is frequently consulted by all types of patients regarding age, social status, or health status. This gives the dentist the chance to possibly discover all kinds of oral lesions and systemic diseases since the dentist is not only obliged to examine the intraoral area including teeth, intraoral tissues, and bone structure but also the extraoral area, like

skin, bone structure, lymph nodes, eyes, and the overall appearance of the patient. This is followed by a proper medical history that includes all information about known systemic diseases, medications, previous operations and family history of diseases. This is aimed to rule out any condition that could risk or influence dental treatments and to create the basis for the diagnostic of oral pathologies or their underlying causing disease.

Since there are diseases that express oral manifestations the dentist can be crucial for an early diagnosis, because they even might be one of the first signs of a systemic disease that are present. Especially an oral biopsy can often lead to clarification of a diagnosis of a disease and can help to rule out possible malignancies. For example in the case of the disease white sponge nervus, which itself is a benign disease, exist numerous potentially malignant differential diagnoses, because of the similarity in appearance, like oral leukoplakia, squamous cell carcinoma or secondary syphilis to name a few [23,24]. With a biopsy can an incorrect diagnosis be prevented and with that an incorrect and unnecessary treatment [24].

After proper intra- and extraoral examination and medical history, a dentist can either establish a diagnosis himself or if necessary, transfer the patient to an adequate physician. Here it is especially important to establish good interdisciplinary communication between professionals, to provide the patient with the best possible health care. For example, does the diagnosis and treatment of Pseudoxanthoma Elasticum as a multisystemic disease [20], demand good communication between multiple specialists such as dermatologists, cardiologists, dentists, pathologists, and ophthalmologists necessary [19,21,22].

Regarding genetic diseases that express oral manifestations further studies should be obtained, since due to the fact that the diseases are all quite rare with a prevalence between 1: 10 000 [10] and 1:200 000 [7], there are not many and sufficient numbers of studies that provide clear and profound information about the oral and systemic manifestations. Studies and case reports sometimes present different information on for example the frequency of oral lesions or they present a very broad range of descriptions of oral signs and symptoms. For example according to previously published articles the frequency of lesions in the oral mucosa in Pseudoxanthoma Elasticum range between 83% and 5% [22].

It is fundamental that precise descriptions of the lesions related to rare genetic diseases are properly studied and described, so they do not get confused with other lesions, for example, oral lesions of Pseudoxanthoma Elasticum often get misdiagnosed as Fordyce granules [19,22], or so that they are not confused with more common diseases, leading to tiresome and unnecessary long journeys to obtain a proper diagnosis. Especially not only because health care provides are not sufficiently trained in rare genetic diseases, or because of a lack of diagnostic tests and missing access to high-cost medicines [28].

Even though rare genetic diseases are an important health problem it is not enough investigated. Only in Europe, it is estimated that 30 million people are affected by rare diseases and every single one of them has a right to be treated competent and sufficiently [28].

5.2. Assessment if oral pathologies of genetic systemic diseases can be used for prevention of the underlying associated pathology/disease.

The early diagnosis of such rare inherited diseases gives the patients not only the opportunity for adequate treatment and management but also the opportunity for prevention of the disease.

If we apply the term prevention to the area of rare genetic diseases it is a broad term, since hereditary genetic diseases are already present in the genes of a person from the very beginning on. It can either mean that a diseased person decides against having children or it can mean that we cure the child even before it is born. Both approaches contain their very own medical, scientific, morally, and socially difficulties. In the first case, we need first of all a patient that was correctly diagnosed and second of all, we need to educate the patient about the risks and possibilities that can occur, becoming a child. The patients need to be provided with sufficient and understandable information for them to make an educated decision about having children or not, depending on the likelihood and the severity of the disease and based on the personal, cultural, religious, and moral values of the patient [29]. This might lead to the decision to get children anyway, to select a healthy embryo by genetic testing, to adopt, or to even stay childless to prevent the transmission of undesired DNA [30].

This kind of prevention is only possible if there is a health care system that is capable of providing patients with rare genetic diseases with an easily accessible possibility for diagnosis or to be detected by screening, being unaware of the condition [29].

Since the information about rare genetic diseases so far is lacking in sufficient amount of data, there is the need for a proper surveillance system that collects enough epidemiological data, further research needs to be done and and in health care system

is necessary that includes genetic counseling, providing affordable and simple genetic testing [29].

Especially against the background that often there is no suitable or specific drug for a rare disease, prevention gains in significance. Only 10% of all rare diseases can be treated with a for the disease specifically developed drug [28]. This is because with the low number of affected people, the economic and financial incentive for pharmacological industries to search for drugs is very low [29].

Furthermore, is the education of the population fundamental. The population needs to be educated about the existence of rare genetic diseases and their risks that they oppose not only to themselves but also the health of their children [29]. All this is necessary so that as many people as possible are aware of their situation.

But there is hope for the future, that there will be other ways of prevention of rare genetic diseases possible. The research around genetics is fast advancing, especially after the human genome project in 2003 was published, making it for the first time ever possible to find the causative genes for mutation-related diseases. Also, the United Kingdom granted the first allowance in the world to research on human embryos, in 2017 [30]. There are promising treatment approaches like splicing modulation therapy as a treatment for genetic diseases. It might be a potentially useful treatment for rare inherited diseases [31]. Additionally is there the European Cooperation of Science and Technology COST providing a network for communication to prevent different researchers all over the world to make the same mistakes, in order to accelerate the research [31].

This gives reasonable hope to be able to correct genes in gametes or early embryos in a future that is not too far ahead [30].

6. Conclusion

6.1 Study of genetic systemic diseases that present an early onset of oral signs and symptoms, their origin, development, and presentation.

The human being is based on the genetic information contained in the DNA, hidden in the cells of every human being. They define every single aspect of our bodies and minds. Unfortunately, can mutations lead to genetic diseases affecting the oral and systemic health of a human being. Many of the diseases are defined as rare genetic diseases, leading to difficulties regarding a proper and certain diagnosis. Therefore to train properly every kind of health care professional, but in particular dentists, five of the most common rare genetic systemic diseases that present early and clear oral manifestations that can be used for an early diagnosis by the dentist were studied, describing their typically oral appearance, systemic affection and genetic cause. They are Hereditary Hemorrhagic Telangiectasia, Peutz-Jehgers Syndrome, Pseudoxanthoma Elasticum, White Sponge Nevus, and Basal Cell Nevus Syndrome.

6.2 Assessment if oral pathologies of genetic systemic diseases can be used to facilitate the diagnosis of the underlying associated pathology/disease.

Highlighted is the close relationship between oral and systemic health, leading to the need of all health care professionals to establish good interdisciplinary communication to provide the patient with the best possible health care. The knowledge about these diseases, their manifestations, and causes, gives the dentist the possibility to establish an early diagnosis, for inducing further steps of diagnosis and treatment of the patient.

6.3 Assessment if oral pathologies of genetic systemic diseases can be used for prevention of the underlying associated pathology/disease.

When patients with rare genetic diseases get the chance to be properly diagnosed by the health care system, creates the ground for prevention. Prevention and further steps can only be initiated when the patient is aware of his condition. Because of the fast advancement of sciences and promising techniques like splicing modulation therapy, there is hope for the prevention of rare genetic diseases in the future. This way 30 million people alone in Europe with rare inherited genetic diseases can be helped to manage their health as well as possible.

7. Responsibility

One of the highest values of life is health. To achieve this, the best possible way is that the health care system unites all its health care professionals to provide the best possible care for patients. Since the human body has to be considered as an overall system, where all organ systems influence each other, it is just logical that all specialized practitioners and also dentists have to work together and additionally that they have to train themselves regarding diseases, their signs and symptoms, that lay outside of their specializations. To identify them correctly, it is necessary to establish a correct diagnosis that not only includes superficially the found manifestations but also the whole body and with that the possible underlying and the manifestation causing the disease. As a result, if necessary, a dentist or physician can induce the right procedure for further diagnosis and with that the right treatment.

Especially regarding the equality of all human beings, it is not only important to reliably diagnose common and highly distributed diseases but also less common diseases. Especially in these cases, patients are frequently undiagnosed or misdiagnosed. And the dentist as a part of the health care system must potentially be able to detect these diseases or at least suspect a potential present rare disease to induce the right diagnostic examinations.

A proper and early diagnosis of a disease is not only the basis for an adequate treatment that ensures the best possible health of a person, but it also holds the possibility of prevention of mild or severe consequences of a disease. This does not only improve the quality of life for an individual but also provides an economic advantage, because possible consequences of a disease can be prevented and with that do not need to be treated in the future. This would lead to health care systems that are less burdened and saves money that can be otherwise invested in the health of the rest of the population.

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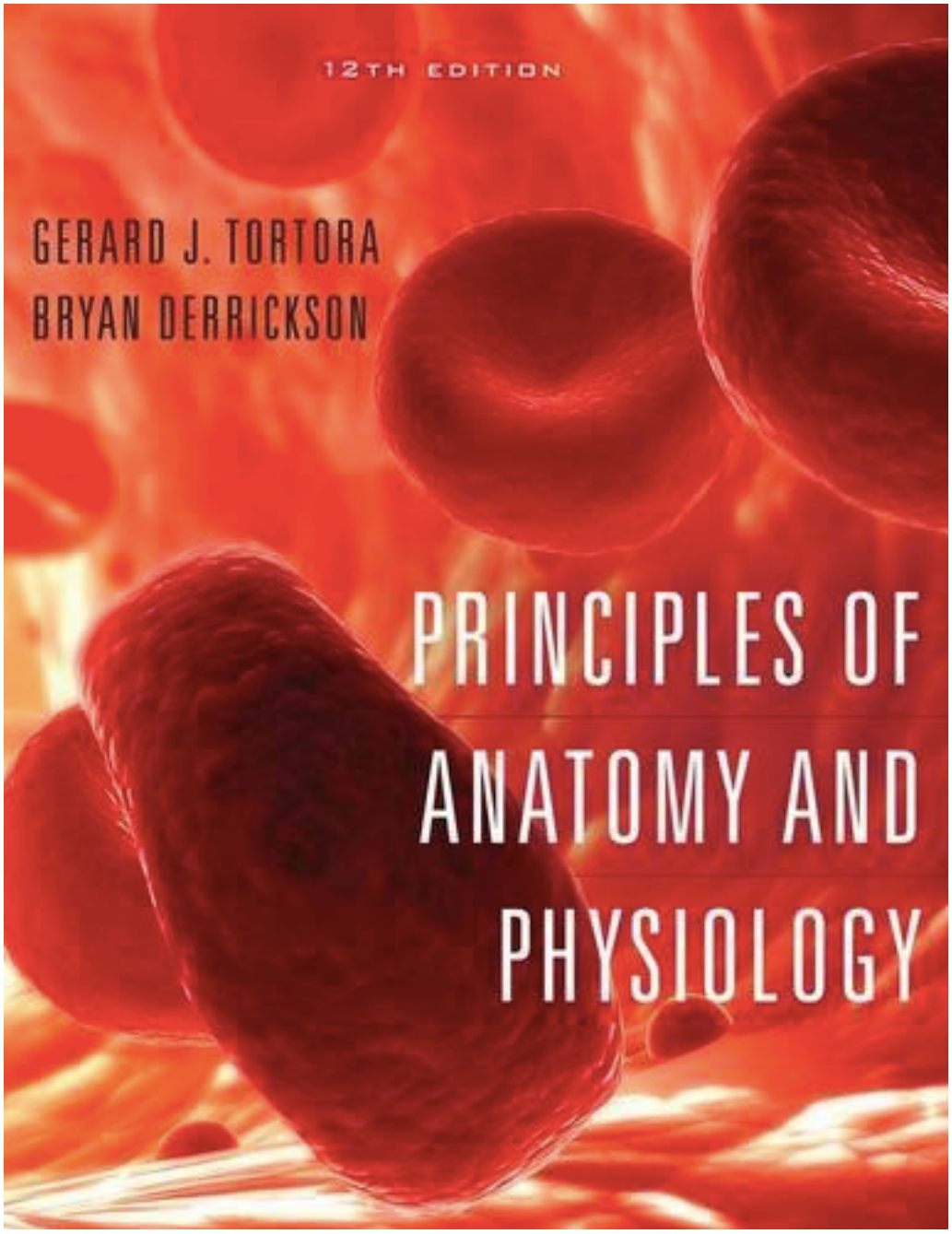
Annex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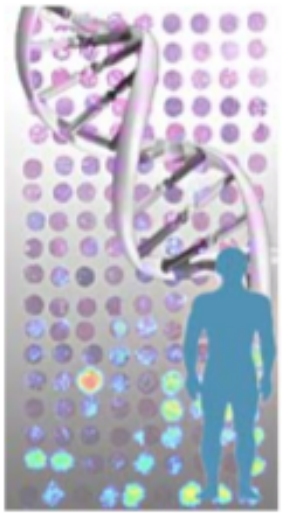

A small piece of human DNA

Human genetics describes the study of inheritance as it occurs in human beings. Human genetics encompasses a variety of overlapping fields including: classical genetics, cytogenetics, molecular genetics, biochemical genetics, genomics, population genetics, developmental genetics, clinical genetics, and genetic counseling. Genes can be the common factor of the qualities of most human-inherited traits. Study of human genetics can be useful as it can answer questions about human nature, understand the diseases and development of effective disease treatment, and understand genetics of human life.

Genetic differences and inheritance patterns

Inheritance of traits for humans are based upon Gregor Mendel's model of inheritance. Mendel deduced that inheritance depends upon discrete units of inheritance, called factors or genes.

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GENETIC TESTING IN ORAL MEDICINE: A NOVEL APPROACH

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Abstract

The modern era has brought in a great revolution in the field of dentistry with use of the genetic tests or DNA based tests. These are the newest and most sophisticated techniques with the ability to detect the risk of occurrence of diseases from the rarest to the most common. With the successful completion of the human genome project in 2003, there was abundance of genetic information concerning our biological make up and thus began the quest to obtain biologic explanations of health, disease and wellness at cellular level. The rapid pace of discovery fueled expectations that genetic information could be integrated into clinical care paradigm and this technology became a new ray of hope. The field of dentistry is no exception to this. The Human genome sequence and annotation provided an increasingly detailed description of oral, dental, and craniofacial diseases and disorders at the molecular level thereby increasing the scope for use of sophisticated genetic testing methods in oral diseases. Hence it is imperative for oral clinicians to understand the various aspects, practical application and limitations of genetic tests. This paper aims to overview genetic testing and its practical relevance in the field of oral health care.

Keywords: genetic testing, human genome, dentistry, practical applications, limitations

Introduction

Genetic testing is defined as "tests performed to determine if an individual has certain gene changes in the form of mutations or chromosomal alterations predisposing him/her to a particular health condition, or to confirm the diagnosis of a genetic disorder." This technique involves direct examination of DNA typically taken from cells in a sample of blood, body fluids or tissues to identify changes within genes. As suggested by the Task Force on Genetic Testing (http://www.genome.gov/19516567), genetic testing can include any test (molecular, cytogenetic, or biochemical) providing information derived from the human genome and its expression. [1] With this information it is possible to

Registro: 1

Título: Human Genome Project.

Fuente: Columbia Electronic Encyclopedia, 6th Edition. 2020, p1-1. 1p.

Tipo de documento: Reference Entry

Palabras clave proporcionadas por el autor: GENETICS1

Resumen: Human Genome Project, international scientific effort to map all of the genes on the 23 pairs of human chromosomes and, to sequence the 3.1 billion DNA base pairs that make up the chromosomes (see nucleic acid). Begun in 1990 with the goal of enabling scientists to understand the basis of genetic diseases and to gain insight into human evolution, the project was largely completed in 2000 when 85% of the human genome was decoded, and ended in 2003 with 99% decoded; detailed analyses of all the pairs were published by 2006. In the process, scientists identified genes for cystic fibrosis, neurofibromatosis, Huntington's disease, and an inherited form of breast cancer. In addition, the project decoded the genome of the bacterium E. coli, a fruit fly, and a nematode worm (see phylum Nematoda), in order to study genetic similarities among species, and a mouse genome was also decoded. [ABSTRACT FROM PUBLISHER]

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Human Genome Project

Human Genome Project, international scientific effort to map all of the genes on the 23 pairs of human chromosomes and, to sequence the 3.1 billion DNA base pairs that make up the chromosomes (see nucleic acid). Begun in 1990 with the goal of enabling scientists to understand the basis of genetic diseases and to gain insight into human evolution, the project was largely completed in 2000 when 85% of the human genome was decoded, and ended in 2003 with 99% decoded; detailed

What are the types of genetic tests?

From Genetics Home Reference. Learn more

Genetic testing can provide information about a person's genes and chromosomes. Available types of testing include:

Newborn screening

Newborn screening is used just after birth to identify genetic disorders that can be treated early in life. Millions of babies are tested each year in the United States. All states currently test infants for phenylketonuria (a genetic disorder that causes intellectual disability if left untreated) and congenital hypothyroidism (a disorder of the thyroid gland). Most states also test for other genetic disorders.

Diagnostic testing

Diagnostic testing is used to identify or rule out a specific genetic or chromosomal condition. In many cases, genetic testing is used to confirm a diagnosis when a particular condition is suspected based on physical signs and symptoms. Diagnostic testing can be performed before birth or at any time during a person's life, but is not available for all genes or all genetic conditions. The results of a diagnostic test can influence a person's choices about health care and the management of the disorder.

Carrier testing

Carrier testing is used to identify people who carry one copy of a gene mutation that, when present in two copies, causes a genetic disorder. This type of testing is offered to individuals who have a family history of a genetic disorder and to people in certain ethnic groups with an

For more information about the uses of genetic testing:

Johns Hopkins Medicine provides additional information about genetic carrier screening.

The National Society of Genetic Counselors provides an overview of the different types of genetic testing that are available.

The Centre for Genetics Education offers an overview of prenatal testing, as well as fact sheets about preimplantation genetic diagnosis, screening tests during pregnancy, and diagnostic tests during pregnancy.

EuroGentest provides fact sheets about predictive testing and

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Dentists' awareness about the link between oral and systemic health

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Abstract:

BACKGROUND: Oral health is integral to systemic health. There is a growing body of evidence of an association between periodontal and systemic diseases. The aim of the study was to evaluate the awareness of dentists regarding link between oral and systemic health.

MATERIALS AND METHODS: Data was collected using a self-administered pilot-tested questionnaire. Dentists awareness about link between oral and systemic link was assessed on five point likert scale. Data was entered and analysed using SPSS.

RESULTS: Of the 588 dentists, 500 completed the questionnaire (response rate 85.03%). About 93% of the participants (mean age 25.82 ± 4.21 years) agreed that oral health was associated with systemic health. Most dentists were aware of a connection between periodontal disease and diabetes (84.4%) and heart disease (70.2%). Similarly, 85.6% believed in the negative impact of oral disease on the quality of life of patients. More female than male dentists were aware of the relationship between periodontal disease and adverse pregnancy outcomes, diabetes, and rheumatoid arthritis ($P < 0.001$). Most dentists (97%) believed that more patients would seek oral care if they were aware of the oral-systemic link. After adjustments, private dentists were 4.65 times more likely than public dentists to believe in improving access to oral care with increased patient awareness of the oral-systemic connection ($P = 0.011$).

CONCLUSIONS: Most dentists were aware of the oral-systemic link. They believed that patients' access to oral care would improve if they were aware of a connection between oral and systemic health. Therefore, patients should be informed of the oral-systemic link to improve their oral health.

Keywords:

Dental professionals, oral care, oral health, systemic health

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Introduction

The associations between oral disease particularly periodontal disease and chronic systemic diseases such as diabetes, coronary artery disease, adverse pregnancy outcomes, and rheumatoid arthritis (RA) have been reported in observational and clinical studies.[1-4] It has been suggested that inflammatory cascade initiated by the mediators in periodontal disease can cause oral microbes, lipopolysaccharides, and proinflammatory molecules to gain access to different parts of the body, thus contributing to chronic systemic conditions and infectious diseases.[5] *Porphyromonas gingivalis*, a periodontal bacterium, has been identified as a potent agent responsible for vascular and atherosclerotic changes in cardiovascular disease.[6] Similarly, DNA analysis of synovial joint fluid of rheumatoid arthritis (RA) patients demonstrated periodontal pathogens, suggesting their role in the etiology of RA.[7] There is a bidirectional relationship between periodontal disease and diabetes mellitus. Diabetes is a strong risk factor for periodontal disease, while uncontrolled periodontal condition can enhance insulin

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Oral Signs of Genetic Disease

11

Julio C. Sartori-Valinotti and Jennifer L. Hand

Incontinentia Pigmenti (Bloch-Sulzberger Syndrome)

Epidemiology

Incontinentia pigmenti (IP) is an ectodermal dysplasia with an estimated prevalence of 0.7 cases per 100,000 births, almost exclusively affecting females [1].

Etiopathogenesis

IP is an X-linked disease caused by mutation in the IKK-gamma gene (inhibitor of nuclear factor kappa-B kinase subunit gamma), previously known as NEMO, located on chromosome Xq28. Disruption, usually by deletion, of the IKK-gamma gene is responsible for downstream activation of cellular apoptosis. Programmed cell death in different tissues such as the skin, teeth, nails, eyes, skeleton, and central nervous system (CNS) accounts for the clinical manifestations of the disease. The disease is lethal in males, usually prenatally.

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Clinical Manifestations

In affected females, the striking cutaneous findings evolve sequentially in four distinct, overlapping stages that follow developmental skin lines (Fig. 11.1):

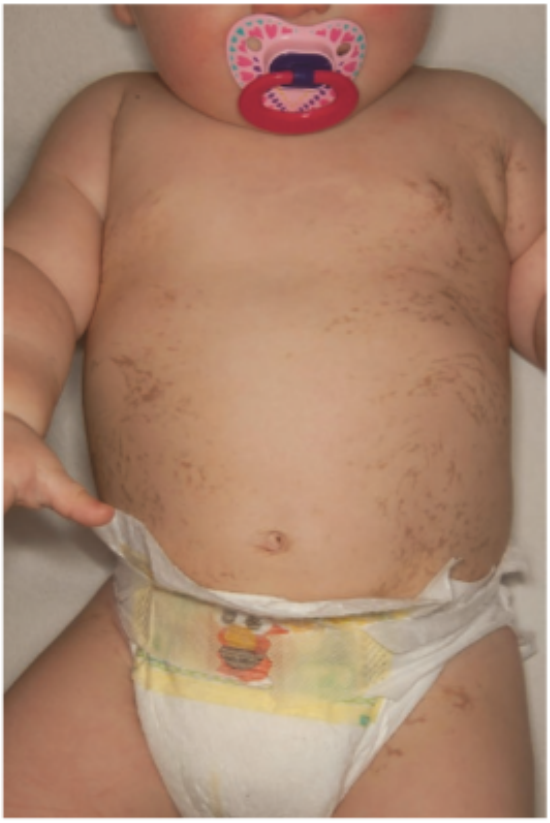

Fig. 11.1 Female infant with cutaneous hyperpigmentation along developmental skin (Blaschko's) lines, typical of incontinentia pigmenti

ESSENTIALS OF DIAGNOSIS

- Recurrent epistaxis.
- Mucocutaneous telangiectases.
- Visceral arteriovenous malformations (especially lung, liver, brain, bowel).

CLINICAL FINDINGS

A. Symptoms and Signs

Hereditary hemorrhagic telangiectasia (HHT), formerly termed "Osler-Weber-Rendu syndrome," is an autosomal dominant disorder of development of the vasculature. Epistaxis may begin in childhood or later in adolescence. Punctate telangiectases of the lips, tongue, fingers, and skin generally appear in later childhood and adolescence. Arteriovenous malformations (AVMs) can occur at any age in the brain, lungs, and liver. Bleeding from the gastrointestinal tract is due to mucosal vascular malformations (eFigures 40–7 and 40–8) and usually is not a problem until mid-adult years or later. Pulmonary AVMs can cause hypoxemia (with peripheral cyanosis, dyspnea, and clubbing) and right-to-left shunting (with embolic stroke or brain abscess). The criteria for diagnosis require presence of three of the following four features: (1) recurrent epistaxis, (2) visceral AVMs, (3) mucocutaneous telangiectases, and (4) being the near relative of a clearly affected individual. Mutation analysis can be used for presymptomatic diagnosis or exclusion of the worry of HHT.

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Short Case Report

Hereditary hemorrhagic telangiectasia, embolization, and Young's procedure: oral surgical management

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Keywords: telangiectasia / hereditary hemorrhagic / epistaxis / therapeutic embolization

Abstract – Hereditary hemorrhagic telangiectasia (HHT) case with history of embolization and Young's procedure: surgical management. **Introduction:** Osler–Weber–Rendu disease hereditary hemorrhagic telangiectasia (HHT) is a genetic vascular dysplasia. It causes hemorrhagic manifestations, cutaneous and mucosal telangiectasia and visceral vascular shunts, which sometimes lead to brain abscesses after dental avulsion. Acute epistaxis can be managed by vascular ligature or selective embolization. In rare cases, management can even go as far as nasal closure. **Observation:** A case of five dental avulsions is described, in a patient affected by HHT who previously underwent a bilateral embolization in the area of the facial artery as well as Young's procedure for frequent epistaxis. **Comments-Conclusion:** The management of patients affected by HHT needs rigorous hemostatic methods and outpatient postoperative monitoring. Additionally, the remarkable imaging from panoramic radiography used in this case was instrumental in keeping track of embolization, by clearly highlighting the arterial pathways.

Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler–Weber–Rendu disease (OWRD), is an autosomal dominant genetic disease. Its incidence is 1 person out of 5 000 [1]. It is linked to an angiogenesis disorder that causes arteriovenous malformations and frequent epistaxis [2]. It exposes the patient to an increased hemorrhagic risk that needs to be factored in during surgical intervention. Certain treatments for such hemorrhages can also have wider implications for dental care, as in the reported case.

Clinical observation

A 58-year-old patient came to the odontology department for a consultation for tooth mobility and gingival hemorrhaging. He was diagnosed with HHT at age 35 years, which was discovered after repeated epistaxis. His medical treatment consisted of an antifibrinolytic (tranexamic acid oral, 1 g three times a day). A bilateral embolization in the vicinity of the facial artery was performed five years before and a Young's operation (surgical closure of the nasal cavity) 3 years before (Fig. 1). Despite these interventions, the patient was hospitalized many times for severe epistaxis, and he received iron infusions. An oral cavity examination revealed generalized chronic periodontitis, requiring the avulsions of five teeth: 14, 15, 16, 25, and 26. The surgery was performed in the operating room of the Ambulatory Surgery Unit to facilitate postoperative monitoring. The avulsions were performed under local anesthesia and conscious sedation. Antibiotic prophylaxis was administered, and the following hemostatic methods were implemented:

- collagen compresses in the nasal vestibules;
- interrupted sutures;
- biological thrombin + fibrinogen glue;
- then, compression with tranexamic acid.

The complete blockage of the nasal cavity (Fig. 2) forced the anesthetic team to modify the method of oxygenation. The nasal cannula was positioned near the oral cavity.

The patient also received periodontal and prosthetic care, followed by regular follow-up to decrease the risk of bleeding and bacteremia.

Discussion

HHT, also called OWRD, is a constitutional vascular dysplasia. It is a rare genetic disease, affecting approximately 1 in 5 000 individuals [3]. Its diagnosis is primarily clinical and

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CASE HISTORY REPORT

ABSTRACT

Hereditary hemorrhagic telangiectasia (HHT) is an inherited mucocutaneous disease characterized by recurrent epistaxis, lesions on skin and oral mucosa, and arteriovenous malformations of the soft tissues.

This article describes the treatment of a 64-year-old woman with a bleeding nodule, which was diagnosed as an arteriovenous malformation of the gingival mucosa. She was treated using sclerotherapy. Patients with HHT can be treated in the dental office and vascular malformations of these patients can be successfully managed with sclerotherapy, which eliminates the need for invasive surgical procedures and the possibility of postsurgical complications.

KEY WORDS: telangiectasia, Osler-Weber-Rendu syndrome, arteriovenous malformation, sclerotherapy

Oral vascular malformation in a patient with hereditary hemorrhagic telangiectasia: a case report

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Introduction

Hereditary hemorrhagic telangiectasia (HHT), also called Osler-Weber-Rendu syndrome, is an inherited mucocutaneous disease produced by mutation on endoglin and ALK genes.[1] This disease can present in five types,[2] the most prevalent being type I, produced by mutation on the endoglin gene (9q34.1), and type II, caused by a mutation in activin A Receptor type II-like 1 on chromosome 12 which encodes ALK1 (12q11-q14). Proteins produced by these genes are important for endothelial wall integrity, modulating different cell processes including migration, proliferation, adhesiveness, composition, and organization.[3]

HHT is characterized by telangiectatic lesions of 1 mm to 2 mm located in the oral mucosa, lips, and fingers; patients may have a family history of disease; episodes of recurrent spontaneous epistaxis; or arteriovenous malformations in the lungs, gastrointestinal tract, liver, brain, and spinal cord.[4] Diagnosis of HHT is "definite" if a patient presents three of those characteristics, "suspect" if two are present, and "unlikely" if only one characteristic is present.[2] These criteria permit increased levels of clinical suspicion without leading to overdiagnosis, as a definitive diagnosis requires the presence of specific soft tissue lesions or a family history of HHT, because nosebleeds and some telangiectasia are common in the general population.[2]

Disease manifestations are caused by vascular abnormalities of arterioles, capillaries, and venules, which have diminished smooth muscle walls and practically no elastic fibers. As the lesion develops, blood vessels become dilated and filled with blood, lose contractile function, are more prone to disruption, and have increased risk of hemorrhage.[5] Patients may have repeated episodes of nasal bleeding that may lead to anemia.[6]

Patients who have HHT may also experience intense bleeding from toothbrushing, a result of the diminished vascular wall thickness associated with inflammation caused by poor oral health and gingival disease.[7] Hemorrhagic ulcers and vesicles on the gingival and oral mucosa may also be present.[8] Although the prognosis for HHT is good, patients who are not aware of their condition can have significant morbidity. In such cases, mortality ranges between 1% for patients with epistaxis, and 10% for patients with cerebral abscesses.[9]

Case report

A 64-year-old Caucasian woman presented to the Piracicaba Dental School's Oral Diagnosis Clinic with the chief

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CLINICAL APPROACH TO HEREDITARY HEMORRHAGIC TELANGIECTASIA

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ABSTRACT

Background: Hereditary hemorrhagic telangiectasia (HHT or Rendu-Osler-Weber disease) is a rare syndrome, inherited as an autosomal dominant trait with incidence of 1/10000. The clinical manifestations are due to vascular malformations and predisposition to hemorrhages in different organs, the leading symptom being recurrent epistaxis. If diagnosed with HHT, the patient and his relatives and especially children have to be screened for occult vascular malformations.

Case report: A 30 years old woman was treated for cerebral stroke, epistaxis, anemia, arterio-venous malformations for over 6 months. Only at this point she was diagnosed with HHT, after noticing the typical mucosal changes. Focused family history revealed symptoms of HHT in her only child, her father, aunt and two cousins. The child was screened for occult vascular malformations – attainment of the nasal mucosa, lungs, gastrointestinal system, liver and brain. Pulmonary and gastrointestinal arterio-venous malformations were proven.

Conclusion: Any case of recurrent epistaxis should be evaluated for HHT. After confirmation of the diagnosis every patient and close relatives have to be screened for attainment of other organs and followed up in order to prevent severe life threatening complications.

Key words: hereditary hemorrhagic telangiectasia; epistaxis; screening;

BACKGROUND:

Hereditary hemorrhagic telangiectasia (HHT or Rendu-Osler-Weber disease) is a rare disease of the entire vascular system, especially of the capillary vessels. It is inherited as an autosomal dominant trait with incidence of 1/10000 [1, 2].

Clinical manifestation depends on the localization of telangiectases and / or arterio-venous malformations. It is characterised by age related variable expressivity and incomplete penetrance. The most common and typical symptom in 95% of the affected patients is recurrent epistaxis [1, 3]. With variable severity and frequency it occurs at about age of 10/15 [4]. Frequently telangiectasias are observed (up to 95% of the affected) being present at places like skin, hands, face and mouth. Less frequent, but more dangerous is bleeding from the gastrointestinal tract (up to 25%). Up to 50% of the affected suffer from lung AV malformations predisposing to early hemorrhagic or ischemic strokes. AV cerebral malformations are rare (5-20%), but they are also life-threatening. There are also changes in the liver and spinal cord, but they are more difficult to be diagnosed because of their rare bleeding and less frequent complications.

The Curacaocriteria are in clinical use for diagnosis of HHT [2]. It is considered:

Definite when three or more of the criteria below are present

Possible or suspected when two of the criteria below are present

Unlikely when fewer than two of the criteria below are present

- Epistaxis: spontaneous and recurrent
- Telangiectases: multiple on face, lips, oral cavity and fingers
- Visceral AVMs (pulmonary, cerebral, hepatic, spinal and/or gastrointestinal)
- Family history

Molecular diagnosis

Because of locus and allelic heterogeneity confirmation of the diagnosis at the molecular level is complicated. Mutations in two genes HHT1 and HHT2, respectively located in chromosome 9 and 12 are associated with the disease [2, 5], but there are also other, yet undiscovered genes. Mutations in the SMAD4 gene cause syndrome that combine HHT and juvenile polyposis [2]. Until now, the known genes are five or six.

AIM:

The aim of the study is to present a case of a family with epistaxis in three generations and to discuss the clinical approach

Neurovascular screening in hereditary haemorrhagic telangiectasia: dilemmas for the paediatric neuroscience community

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Hereditary haemorrhagic telangiectasia (HHT) is a dominantly inherited disorder characterized by mucocutaneous telangiectasias and arteriovenous malformations (AVM) in multiple organs, with a frequency of at least 1 in 10 000.[1] The most common manifestations are epistaxis, characteristic telangiectasias, and gastrointestinal haemorrhage.[2] Neurological features include pial AVM (nidal and micro [nidus <1cm] AVM), high-flow arteriovenous fistulae (AVF) in the brain and spinal cord, capillary telangiectasias,[3] and also cerebral ischaemia or abscess due to paradoxical emboli arising via pulmonary vascular shunts. Cerebrovascular malformations (AVM/AVF) affect up to 14% of the HHT population.[2] Recent clinical guidelines recommending neurovascular screening[4] means that it is timely for awareness of HHT, and the complexities of clinical and genetic diagnosis, to be raised in the paediatric neuroscience community.

Diagnosis of this disorder remains primarily clinical (Table I); individual features carry differential weight in terms of predictive diagnostic power. Three genes have been identified: *endoglin* (HHT1; OMIM 187300), *ACVRLK1* (HHT2; OMIM 600376; which together account for most genetically characterized cases), and *SMAD4* (juvenile polyposis/hereditary haemorrhagic telangiectasia syndrome [JPHT] OMIM 175050), with many mutations described. These genes are components of the transforming growth factor beta and bone morphogenic protein signaling pathways.[5,6] Two further loci have been assigned HHT3 (OMIM 601101) and HHT4 (OMIM 610655).

Where the diagnosis is beyond reasonable clinical doubt, mutations are detected in 87 to 93% of affected individuals.

Table I: Curaçao criteria[4]

Epistaxis	Spontaneous/recurrent
Telangiectases	Multiple; lips/nose/oral cavity/fingers
Visceral lesions	Gastrointestinal telangiectasia, pulmonary, hepatic, cerebral or spinal arteriovenous malformation
Family history	Affected 1st degree relative

'Definite' HHT=3 or more criteria; 'possible' HHT=2 criteria; 'unlikely' HHT if 0 or 1 criteria. HHT, hereditary haemorrhagic telangiectasia.

However, this leaves a significant proportion with a 'definite' clinical diagnosis, and a larger number with a 'possible' diagnosis (Table I legend), without an identified mutation. A combination of epistaxis and family history alone is not a reliable indicator of diagnosis and characteristic skin lesions are rarely present in childhood. Penetrance is age dependent[6,7] and children are therefore unlikely to show sufficient features for a clinical diagnosis. This means that, unless genetic testing is informative, all children of a parent with HHT are considered to have possible HHT, even without any phenotypic manifestations.

Some of the excess mortality in HHT, especially in young people, has been attributed to haemorrhage from brain AVMs (BAVMs)[2] but data is scant, with a likely ascertainment bias.[3,7] BAVMs are more commonly associated with mutations in *endoglin* than *ACVRLK1*, with frequencies of 8 to 14% in the former compared with 2 to 3%.[8,9] The suggestion that BAVMs in HHT may carry a lower haemorrhage risk than sporadic BAVMs remains contentious.[10] Although BAVMs are usually considered congenital,[3] as vascular lesions in HHT are thought to represent an aberrant response to angiogenic stimuli[2] and spontaneously regressing AVMs have been documented,[11] it seems likely that there is also a dynamic component, further supported by frequent presentations during pregnancy.[10] It has been suggested that early mortality associated with high-flow AVF explains the discrepancy in age of presentation between these (infancy/early childhood[3]) and nidal/microAVM (adolescents/young adults); however, overall, high-flow AVFs remain a rare feature of HHT.

ARGUMENTS FOR AND AGAINST NEUROVASCULAR SCREENING FOR CHILDREN WITH HHT

Recent international clinical guidelines recommend screening children with definite and possible HHT for cerebrovascular malformations,[4] using brain magnetic resonance imaging (MRI) with contrast from 6 months of age or when reviewed. This extends to all children of a parent with HHT, half of whom will be unaffected. The potential benefits and hazards of screening for an asymptomatic disease are complex, but in principle, screening is justified if there is effective presymptomatic treatment. In this context, treatment may be any combination of surgery, endovascular embolization, or irradiation, all of which carry significant morbidity and mortality. For example, Krings et al.[12] achieved endovascular obliteration in 38.7% of children with HHT and high-flow pial AVFs, with 6.5% mortality and a similar rate of new neurological deficits. Whilst some BAVMs can be cured, at least 10% may only be amenable to partial treatment and this may encourage evolution to more unfavourable morphologies.[13] Once a lesion is detected, this will, even if asymptomatic, cause considerable anxiety, especially if treatment options are limited.

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Morbus Osler

Mehr als nur Nasenbluten

Anamnese

Eine 72-jährige Patientin stellte sich mit Belastungsdyspnoe im New-York-Heart-Association(NYHA)-Stadium III sowie mit Angina pectoris in unserer Klinik vor. Die Symptome bestanden seit 3 Jahren und zeigten einen progredienten Verlauf. An Vorerkrankungen war nur eine arterielle Hypertonie bekannt, die mit einer täglichen Dosierung von 5 mg Ramipril behandelt wurde. Bei der Patientin lag eine angeborene Symbrachydaktylie der rechten Hand vom peromelen Typ vor (**Abb. 1**).

Körperlicher Untersuchungsbefund

Die Patientin zeigte einen altersentsprechend normalen Allgemein- und Ernährungszustand (Körpergewicht 73 kg, Körpergröße 175 cm, Body-Mass-Index 24 kg/m²). An den Lippen und Wangenfielen Teleangiektasien auf (**Abb. 2**). Auskultatorisch wurde ein spindelförmiges 2/6-Systolikum mit Punctum maximum im zweiten Interkostalraum links parasternal festgestellt. Die weitere körperliche Untersuchung zeigte keine Auffälligkeiten, die die Beschwerden der Patientin erklärten. *Blutbild, Retentionsparameter und Routinelaborparameter* lagen im Normbereich.

Transthorakale Echokardiographie

Zur weiteren Abklärung wurde eine transthorakale Echokardiographie (TTE) durchgeführt. Der linke Ventrikel zeigte eine normale Ejektionsfraktion von 65 % nach Simpson. Der rechte Vorhof und der rechte Ventrikel wiesen eine leichtgradige Dilatation auf. Es bestanden lediglich eine leichte Mitralklappen- und Trikuspidalklappeninsuffizienz, jedoch mit einem rechtsventrikulären Druck von 50 mmHg (Normbereich [NB]: <30 mmHg). Zur Darstellung eines vermuteten Shuntvitiums wurde darauf eine transösophageale Untersuchung durchgeführt. Diese ergab ein persistierendes Foramen ovale (PFO) mit einem spontanen Links-rechts-Shunt, der in einer folgenden invasiven Messung evaluiert werden sollte.

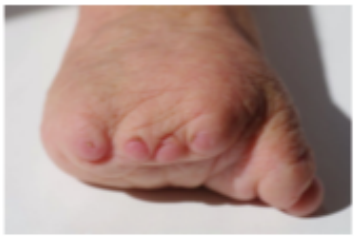

Abb. 1 ▲ Peromele Symbrachydaktylie der rechten Hand (intrauterine Stumpfbildung, meist durch virale Infektionen, Vitaminmangel oder – als bekanntestes Beispiel – durch eine Embryopathie nach Contergan-Einnahme). Bei der Patientin war die Ursache unbekannt. Es bestand kein nachweisbarer kausaler Zusammenhang zur Grunderkrankung

Herzkatheteruntersuchung

In der Koronarangiographie konnte eine koronare Herzkrankheit ausgeschlossen werden. Der linksventrikuläre enddiastolische Druck (LVEDP) war mit 22 mmHg (NB: 6–11 mmHg) erhöht. Es zeigte sich das Bild einer diastolischen Dysfunktion. Zudem konnte eine schwere postkapilläre pulmonalvenöse Hypertonie mit einer Rechtsherzbelastung gemessen werden: mittlerer pulmonalarterieller Druck von 47 mmHg (NB: <15 mmHg); mittlerer „pulmonary capillary wedge pressure" von 36 mmHg (NB: <12 mmHg); mittlerer Druck im rechten Vorhof von 16 mmHg (NB: <5 mmHg; s. rechte Tabelle in **Abb. 3**). Die hämodynamischen Messungen ergaben einen Links-rechts-Shunt von 59 % (Qp/Qs 2,5; im Vergleich zu einem ausgeglichenen Verhältnis von Qp/Qs = 1, wenn kein Shuntvitium vorliegt).

Da das in der TTE festgestellte PFO für das massive Shuntvolumen nicht verantwortlich sein konnte und auch keine fehlmündenden Pulmonalvenen oder ein pulmonaler Shuntfluss festzustellen

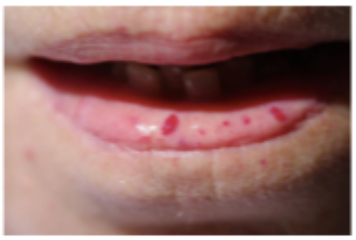

Abb. 2 ▲ Teleangiektasien der Lippe

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Case Report

Angular cheilitis and oral pigmentation as early detection of Peutz-Jeghers syndrome

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ABSTRACT

Background: *Peutz-Jeghers syndrome (PJS) is an inherited autosomal dominant disease determined by a mutation localized at 19p13.3 characterized by the occurrence of gastrointestinal hamartomatous polyps in association with mucocutaneous hyperpigmentation. The manifestation of PJS may first be encountered by a dentist during routine examination due to the presence of pigmented spots in the oral cavity.* ***Purpose:*** *To prevent a high risk of PJS, the dentist must establish its oral manifestation through early detection.* ***Case:*** *A 14-year-old male patient attended complaining of a week-long pain at the corners of the lips. An extra-oral exam revealed fissure lesions, redness, white crust and pain. The patient had experienced bleeding in his bowel movements, abdominal pain, nausea and vomiting since childhood. A number of black, painless, macular lesions, some 1-3 mm in diameter, were present on the upper lips, lower lips, fingers and palms.* ***Case management:*** *The patient was referred for a complete blood count check. The results obtained confirmed him to be suffering from severe anemia and he was, therefore, referred to an internist for treatment for PJS.* ***Conclusion:*** *It can be concluded that the early detection of PJS is crucial in order that the patient receives prompt treatment.*

Keywords: *anemia; gastrointestinal polyps; hyperpigmentation; malabsorption; Peutz-Jeghers syndrome*

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INTRODUCTION

Peutz-Jeghers syndrome (PJS) is an inherited autosomal dominant disease determined by a mutation localized at 19p13.3. PJS results in polyps and mucocutaneous pigmentation evident since childhood or early adulthood.[1,2] In the United States, PJS is a rare disease with an incidence rate of between one case per 60,000 people and one case per 300,000 people. PJS has a prevalence of 1 in 120,000 live births, irrespective of race or gender. The mutant gene STK11 (also known as LKB1) is located at 19p13.3. STK11 is a tumor-suppressing, germline mutation gene which is documented in up to 70–80% of patients with PJS and as many as 15% of cases show complete or partial eradication of STK11.[3-5]

Diagnosis of PJS is based on clinical findings and the histopathological patterns of polyps. Histologically, these lesions show increased basiler melanin without a rise in the number of melanocytes.[5] The manifestation of PJS may first be encountered by a dentist during routine examination in the form of pigmented spots in the oral cavity. Round, oval or irregular, 1-5 mm diameter patches of brown or almost black pigmentation, irregularly distributed throughout the oral mucosa, gums, hard palate and lips are observed. The pigmented facial maculae, particularly encountered around the nose and mouth, are smaller.[1,6] Melanotic macules may be present in other body parts including the extremities, rectum, intranasal mucosa and conjunctiva.[6] The intensity of macular pigment is unaffected by exposure to sunlight. Fading or disappearance of the spots is usually observed in older age.[5,7]

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Clinical Case Report

Medicine

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Early onset Peutz–Jeghers syndrome, the importance of appropriate diagnosis and follow-up

A case report

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Abstract

Rationale: Peutz–Jeghers syndrome (PJS) is currently defined as an inherited condition, also called a familial hamartomatous polyposis syndrome, characterized by the association between pigmented mucocutaneous lesions and hamartomatous polyps in the gastrointestinal tract, especially in the small bowel.

Patient concerns: We present the case of a 7-year-old male patients, diagnosed at the age of 3 years with PJS due to a surgical intervention for acute abdominal pain that revealed a rectal polyp associated with hyperpigmented maculae on the lips and oral mucosa. His family history revealed the same condition in his mother, who was diagnosed much later, at the age of 25 years.

Diagnoses: The upper and lower digestive endoscopy revealed multiple polyps of different sizes within the stomach, and 2 polyps at 5 cm from the anal orifice. The barium enterography revealed 3 polyps within the ileum.

Interventions: We administered blood transfusions and both recto-anal polyps were surgically removed.

Outcomes: The outcome was favorable and the patient was discharged with the recommendations for clinical assessment at least every 6 months, annual laboratory tests, but also follow-up of the detected polyps and screening by upper digestive endoscopy, barium enterography and colonoscopy every 2 years.

Lessons: Early onset of PJS presenting with polys is quite rare since they require time for their development manifesting usually after the first decade of life. Close monitoring is essential for PJS in order to prevent potential complications and early detect the development of related malignancies.

Abbreviation: PJS = Peutz–Jeghers syndrome.

Keywords: diagnosis, follow-up, Peutz–Jeghers syndrome

1. Introduction

Connor and Hutchinson were the first that reported and illustrated Peutz–Jeghers syndrome (PJS) in a pair of identical twins who presented melanotic macules in 1895 and 1896, respectively.[1,2] Nevertheless, the first publication of PJS belonged to Peutz approximately 35 years later, in 1921, defining the condition in a Dutch family as gastrointestinal familial polyposis associated with pigmentations.[3] PJS is currently defined as an inherited condition, with autosomal dominant pattern of transmission, also called a familial hamartomatous polyposis syndrome, characterized by the association between pigmented mucocutaneous lesions and hamartomatous polyps in the gastrointestinal tract, especially in the small bowel.[4] Thus, genetic determinism is essential in the development of PJS similar to other conditions.[5] Hamartomatous polyposis syndromes carry a considerable predisposition to malignancy and they are rare conditions, representing <1% of all inherited gastrointestinal syndromes with increased risk for cancer.[6] Except for PJS, these syndromes also include familial juvenile polyposis syndrome, phosphatase and tensin homolog gene hamartoma tumour syndromes, basal cell nevus syndrome, multiple endocrine neoplasia syndrome 2B, neurofibromatosis type 1, Cronkhite–Canada syndrome, and hereditary mixed polyposis syndrome.[4] Despite the wide variability regarding the prevalence of PJS reported by different studies, most-likely it is of approximately 1 in 100,000 people.[4] Even though it is well-documented that PJG is an inherited, autosomal dominant disorder, its penetrance varies even among the members of the same family. Thus, it is possible for certain members to express only mucocutaneous hyperpigmentation, while others may be found to manifest both hyperpigmentation and hamartomatous

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Peutz-Jeghers syndrome with oral melanosis: Interesting pictures

Sir,

A 28-year-old primigravida mother delivered a male newborn with normal Apgar score of 8/8/9. The mother was a known case of Peutz-Jeghers syndrome, and she had undergone laparotomy for ileal intussusception and had multiple hamartomatous intestinal polyps. She was diagnosed to have a mutation of gene STK11/LKB1 on chromosome 19. Her story was significant with the previous

pregnancy was intrauterine fetal death with hydrops fetalis at 26 weeks of pregnancy. She delivered a history of recurrent intussusception and bleeding per rectum. Physical examination showed hyper pigmented macules over the fingers and oral cavity. Maternal sister also had similar disease with her son expired at age of 6 years because of intussusception and was diagnosed to have intestinal polyps. The neonatal grandmother expired because of pancreatic carcinoma. The index case had pigmentation of the oral cavity with predominance on lower lips [Figure 1]. Pigmentation were dark black in color and involved mucosal surface. The infant was appropriate for gestational age with birth weight of 3.2 kg with head circumference of 35 cm and a distance of 52 cm. The detailed physical examination did not reveal any abnormality except for the presence of accessary nipples. The infant was investigated for Peutz-Jeghers syndrome and was too found to be affected by mutation of STK11/LKB1 genes with mutational analysis showing mutation c. 526G>A, which is a commonly seen mutation in a case of Peutz-Jeghers syndrome. The baby was also assessed with ultrasound of the stomach and renal system, which showed normal study. The baby did not have any melanotic pigmentation over the lips or oral mucous membrane. The child is now under regularly following up. The pedigree chart analysis of the family has been figured in Figure 2.

Discussion

Peutz-Jeghers syndrome is autosomal dominant inherited diseases, which are likewise known by the hereditary intestinal polyposis syndrome. It is characterized by hamartomatous polyps in the gastrointestinal tract (GIT) with hyper pigmented macules on the lips and oral mucosa. It has an incidence of about 1 in 300,000 births.[1] The criteria for diagnosis are deliberately broad.

- Family history of malignant neoplastic disease
- Mucocutaneous lesions
- Hamartomatous polyp in the GIT.

These patients are more probable to develop various GIT tumors, which includes predominantly small intestine, stomach, pancreas, colon, and esophagus.[2,3] These patients have typical muco-cutaneous pigmentation and melanin spots, which take place predominantly in the oral cavity, lips, nostrils, perianal area and digits. Pigmentation of the oral mucosa is pathognomonic of Peutz-Jeghers syndrome and is not associated with other types of dermatologies pigmented lesions.[4,5]

These patients are to be screened regularly for:[6]

- Small intestine with small bowel radiography every 2 years
- Esophagogastroduodenoscopy and colonoscopy every 2 years for colorectal carcinoma
- Computed tomography scan or magnetic resonance imaging of the pancreas yearly for pancreatic carcinoma
- Ultrasound of the pelvis (women) and testes (men) every year for genital tumor
- Mammography (women) from the age of 25 years and continued till life long
- Papanicolaou test every year.

The patients are to be educated about the regular follow-up as these are prone to develop carcinomas in later life.[6,7] Resection of the intestinal polyps is done only when it complicates in from of serious bleeding or intussusception.[8]

Learning points

1. Parents must be counseled intimately about the inheritance and the possibility of disease involvement in the newborn
2. The importance of regular follow-up of the infant should be explained in detail to the parents and the follow-up plan of investigations required should be excused
3. The genetic analysis of the infant should be exercised as it

Figure 1: Facial photograph of the mother with Peutz-Jeghers syndrome. Note: The black spots localized in the perioral mucosal area

Figure 2: Pedigree chart of the family showing autosomal dominant inheritance

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Research Article

Clinical and Genetic Analyses of 38 Chinese Patients with Peutz-Jeghers Syndrome

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Background. Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant inherited disease caused by a germline mutation in the *STK11* gene. It is characterized by mucocutaneous pigmentation, gastrointestinal hamartomatous polyps, and cancer predisposition. *Aims.* We aimed to summarize the main clinical and genetic features of Chinese PJS patients and assessed the genotype-phenotype correlations. *Methods.* Thirty-eight patients clinically diagnosed with Peutz-Jeghers syndrome were included in this study from 2016 to 2019. Combined direct sequencing and multiplex ligation-dependent probe amplification tests were used to detect germline heterogeneous *STK11* mutations. RNA sequencing was performed in polyps of PJS patients and control groups to evaluate the difference in expression of *STK11*. The genotype-phenotype correlations were calculated by Kaplan-Meier analyses. *Results.* All 26 probands and 12 affected relatives had germline heterogeneous *STK11* mutations among which 8 variants were novel. Individuals with missense mutations had their first surgery and other symptoms significantly later than individuals with null mutations. *Conclusion.* This study expanded the spectrum of *STK11* gene mutations and further elucidated individuals with null mutations of *STK11* typically had an earlier onset of PJS symptoms and needed earlier management.

1. Introduction

Peutz-Jeghers syndrome (PJS, OMIM 175200) is a rare inherited autosomal dominant disease, with a triad of mucocutaneous pigmentation (MP), gastrointestinal hamartomatous polyps, and an increasing risk of a wide variety of malignancies [1–3]. The pathological type of PJS polyps is hamartomatous polyp, also known as Peutz-Jeghers-type hamartomatous polyp. Its histopathological features are peculiar branching-tree arrangement of the smooth muscle extending into the lamina propria. The incidence of this disease has been estimated to be 1 in 8,300 to 1 in 200,000 births [4].

The *STK11* (also named *LKB1*) gene mutation is responsible for PJS [5, 6]. It is located on 19p13.3 and comprises 9 coding exons and 1 noncoding exon, coding a member of the serine/threonine kinase family with 433 amino acids [6, 7]. *STK11* is a master tumor suppressor gene that regulates cellular responses involved in cell polarity, energy metabolism, and cell growth via different signaling pathways, including the LKB1/AMPK/mTOR pathway [8–10]. Approximately 80%-94% of PJS patients have germline STK11 mutations detected by direct sequencing and multiplex ligation-dependent probe amplification (MLPA) [11, 12].

The mucocutaneous pigmentation of PJS individuals only affects the appearance and does not require special treatment. The main hazards of PJS are polyp-associated complications, including abdominal pain, gastrointestinal bleeding (GIB), intestinal obstruction, and the occurrence of various malignancies. Patients often come to the hospital because of these symptoms and sometimes need emergency surgery.

Case Report

Seven-Year Follow-Up of Peutz-Jeghers Syndrome

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One of the clinicopathological criteria for diagnosing Peutz-Jeghers syndrome (PJS) is mucocutaneous pigmentation. We present a 57-year-old Iranian female patient with diffuse pigmentation in buccal and labial mucosa. The first colonoscopy revealed one 0.5 cm rectal polyp. However surveillance colonoscopies over a 7-year polyp showed over 100 colorectal polyps.

1. Introduction

Peutz-Jeghers syndrome (PJS) is a rare inherited autosomal dominant disease with an incidence of 1 in 12–30,000 live births, characterized by mucocutaneous pigmentation and multiple hamartomatous polyps in the gastrointestinal tract. PJS patients have a marked increase of risk of developing cancer [1].

A germline mutation in *STK11*, a tumour suppressor gene localized to chromosome 19p13.2–13.3, is an underlying abnormality [2].

The clinicopathological criteria of World Health Organisation (WHO) for diagnosing PJS are as follows:

(1) Three or more polyps, with histological features of PJS.

(2) A family history of PJS with any number of polyps.

(3) A family history of PJS with characteristic mucocutaneous pigmentation.

(4) Characteristic mucocutaneous pigmentation with any number of polyps [3].

To improve the understanding, diagnosis, and treatment of PJS, we now report a case of PJS.

2. Case Present

A 57-year-old Iranian female patient was referred to us (oral medicine specialist), with a chief complaint of pigmentation in oral cavity for more than 15 years.

The patient had scattered dark brown to black macules, most of them measuring <0.5 cm on the buccal and labial mucosa. These pigmentations were asymptomatic and well circumscribed and did not fade under pressure (Figure 1).

There were not any similar macules on the tongue, lips, perioral skin, nostril, hands, and feet. She was previously healthy and took no regular medications. She had no abdominal pain, nausea, vomiting, diarrhea, or history of changing in bowel habits or any significant loss of weight or appetite. In family survey, just her brother had PJS with perioral pigmentation and intestinal polyps compatible with Peutz-Jeghers polyp on histology and without any signs and symptoms of GI diseases, but unfortunately he died in car accident many years ago. Her children (two daughters and one boy) do not have any sign or symptom of this syndrome.

Biopsy of pigmentation on buccal mucosa was performed. Histopathologically there is evidence of increased basilar melanin with melanin incontinence into the submucosa (Figure 2).

The patient with primary diagnosis of PJS was referred to gastroenterologists for more diagnostic assessments.

Correspondence

Cutaneous and oral manifestations of pseudoxanthoma elasticum: clinicopathological features of an uncommon disorder

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Pseudoxanthoma elasticum (PXE), also called Grönblad–Strandberg syndrome, is an autosomal recessive disease associated with mutations in the gene for adenosine triphosphate-binding cassette subfamily C member 6 (*ABCC6*). PXE is characterized by generalized disorders due to accumulation and ectopic calcification in the extracellular matrix, causing degenerative alterations of tissues rich in elastic fibres, through pathogenic mechanisms that are not yet fully elucidated. The prevalence of PXE ranges from 1 in 25 000 to 1 in 100 000 individuals, with a female predilection. PXE can affect various body organs and systems, and is mainly associated with cutaneous, ophthalmic and cardiovascular changes.[1,2] There are few reports of PXE-related oral mucosal findings.[3–5]

A 40-year-old woman presented with skin lesions that had been present since birth. The patient reported that her brother had similar skin lesions and had been diagnosed with PXE. The patient's medical history included urinary incontinence, and pain and difficulty in urinating.

Physical examination revealed asymptomatic, flat, yellowish papules with a cobblestone appearance on the upper chest, axillae, neck, groin and abdomen. On oral cavity examination, diffuse yellowish–white discoloration was noted on the upper and lower labial mucosa and the alveolar mucosa (Fig. 1). The patient also underwent ophthalmic and cardiac evaluation, but no changes were found.

Histological examination of an incisional skin biopsy taken from the chest revealed normal epidermis and a predominance of fragmented, polymorphous and thickened basophilic fibres randomly arranged within the middermis, whereas the papillary dermis and the deep reticular layers remain unchanged. Verhoeff–van Gieson stain confirmed the elastic nature of these fibres and von Kossa stain detected calcium deposits along these elastic fibres (Fig. 2).

Based on these findings, a final diagnosis of PXE was made. Because of the soley mucocutaneous manifestations and the apparent lack of aesthetic concern by the patient, no dermatological treatment was required. The

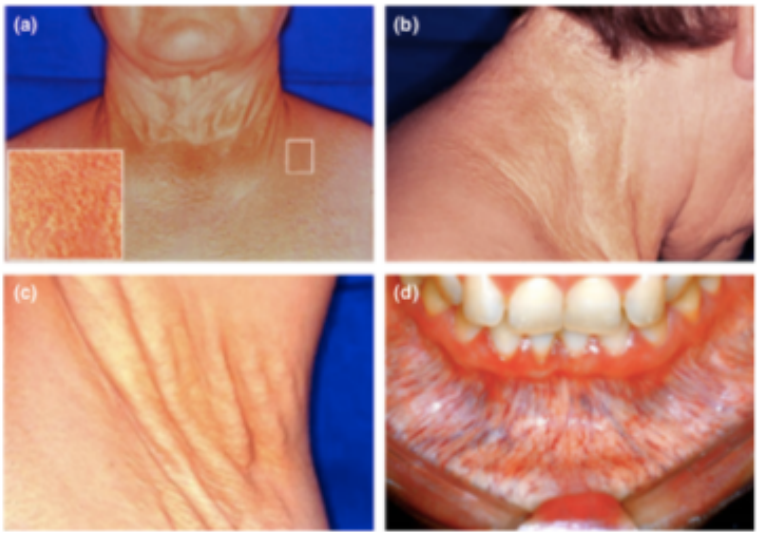

Figure 1 (a–d) Mucocutaneous manifestations in a patient with pseudoxanthoma elasticum: (a) confluent yellowish papules in the cervical and upper chest area, in addition to (b) thickened skin in the neck area and (c) in the axilla. (d) Intra-oral examination, revealed a diffuse yellow–white discoloration in the lower alveolar mucosa.

Case Report

Pseudoxanthoma Elasticum of the Skin with Involvement of the Oral Cavity

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Pseudoxanthoma elasticum (PXE) is an inherited multisystemic disease of elastic fibers that primarily affects the skin and retina. A case of primary PXE of the skin with late involvement of the upper lip is reported. A 55-year-old woman with a previous diagnosis of PXE affecting her skin developed a lesion on her lower lip. An oral examination identified a yellowish macule of undefined limits. A biopsy from her lip was taken and both light and transmission electron microscopies confirmed the presence of fragmented elastic fibers and calcifications on her mucosa, which was compatible with the diagnosis of oral PXE. Since the manifestation of oral PXE is rare in this region, dental practitioners must be aware that this systemic condition may produce oral lesions, which sometimes may mimic other benign diseases of the oral cavity like Fordyce granules. So, the establishment of an appropriate diagnosis is necessary to provide adequate information and attention to the patient.

1. Introduction

Pseudoxanthoma elasticum (PXE) is a multisystemic heritable disease characterized by fragmentation and calcification of elastic fibers [1]. It has been associated with ABCC6-mutation gene, which is responsible for encoding an ATP-dependent transmembrane transporter especially in liver and kidneys [2]. However, the exact mechanism governing its occurrence is heretofore unknown [3, 4]. Classical manifestations include cutaneous yellow papules "pseudoxanthomas [*sic*]", loss of visual acuity, and atherosclerosis, with considerable morbidity and occasional mortality [1, 5]. The prevalence of PXE is estimated range from 1 : 25,000 to 1 : 100,000. However, the real number of cases may be much higher due to the difficulty of accurately establishing its diagnosis [3, 5]. Early PXE detection is extremely important to prevent systemic complications, especially as those seen in the cardiovascular system [6]. Involvement of the oral mucosa has been described in the literature and is potentially useful to the diagnosis of the disease, but little attention has been given in respect to the clinicopathological features of this manifestation in this region [1, 7–9].

To the best of our knowledge only six reported cases of oral PXE have been found in the English literature [7, 8, 10–12]. In this sense, it is worth reporting this case, especially to help dental practitioners in recognition of oral PXE lesions and in establishing an early and correct diagnosis of this life-threatening condition. So, this study describes a case of PXE affecting a woman who developed lesions in the oral mucosa during the progression of the disease and also presents detailed information about clinical, microscopic and ultrastructural aspects of the oral and skin lesions.

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Oral warning signs of elastic pseudoxanthoma

Lara Passos Alvim[1], Thaís Izidoro Pires[1], Maria das Graças Afonso Miranda Chaves[1], Cynthia Savioli[2] and Gisele Maria Campos Fabri[1,2]

Abstract

The pseudoxanthoma elasticum is a multisystemic heritable disease that primarily affects the connective tissue. It has been characterized by fragmentation and calcification of elastic fibers that can lead to complications of skin and cardiovascular system and changes in retina. Involvement of the oral mucosa has been described like white patches striated especially in the mucosa of both upper and lower lips. These oral signs are potentially useful to diagnose the disease, since it is an often undiagnosed disease due to the variability in phenotypic expressions. This study reports a case of pseudoxanthoma elasticum affecting a woman who developed lesions in the oral mucosa during the disease progression. Intraoral clinical assessment revealed the presence of changes mainly in lower labial mucosa and also slightly changes in the mouth floor and the upper labial mucosa. Therefore, the acknowledgment of oral pseudoxanthoma elasticum lesions helps dental practitioners to establish an early and appropriate diagnosis of this disease. This is very important because pseudoxanthoma elasticum is a multisystem disease with morbidity and mortality, and its early diagnosis and also the establishment of a follow-up protocol for these patients could prevent systemic and oral complications.

Keywords

dermatopathology, metabolic disorder, oral lesion, pseudoxanthoma elasticum, systemic complication

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Background

Pseudoxanthoma elasticum (PXE) is a metabolic disorder caused by genetic factors associated with extensive fragmentation and calcification of elastic tissue. It was first described by Jean Darier (1856–1938); however, only in 1929, the ophthalmologist and dermatologist Grönbland and Esther James Strandberg both scored the association of skin lesions with ocular and established the syndrome.[1]

This syndrome was related to the locus located on chromosome 16p PXE 13:01 arm in ABCC6 gene[2] and the mutations in a gene encoding an ABC transporter cause PXE.[3] Mutations within ABCC6 cause reduced or absent transmembranous transport that leads to accumulation of extracellular material. Presumably, this mechanism causes calcification of elastic fibers.[2,4] However, other studies suggest the increased levels of oxidative stress, as observed in fibroblasts of PXE patients, could be an alternative pathological mechanism of disease.[4]

PXE is a rare disease, with estimated prevalence between 1:25,000 and 100,000 inhabitants.[5] This prevalence seems to be highest in South America and it is twice more common among women.[6]

The first manifestation of this disease is in the skin, with the formation of papules and yellowish streaks conglomerate forming little wrinkled appearance and

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Pseudoxanthoma elasticum of the palate: a case report and a brief review of the literature

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Pseudoxanthoma elasticum (PXE), which is a genetic, multi-target disorder characterized by progressive calcification and fragmentation of elastic fibers, affects several organs, including the eyes, skin, and cardiovascular system. Diagnosis of PXE is currently based on cutaneous and ocular signs, histopathologic findings, and a patient's family history. PXE-related oral mucosal lesions are rarely reported, possibly due to the potential for misdiagnosis as Fordyce spots; however, when such lesions are reported, they are primarily localized to the vestibular mucosa of the lower lip. Here, we report the case of a female with an intraoral presentation of PXE at the labial and palatal sites. PXE was previously suspected in this patient because of the presence of cardiovascular, ocular, and cutaneous signs; however, a cutaneous biopsy showed findings not consistent with PXE. Incisional biopsy of the palatal lesion confirmed the PXE diagnosis, leading to proper management of the disorder to prevent ophthalmologic and cardiovascular complications. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;121:e6-e9)

In 1896, J. F. Darier coined the term "pseudoxanthoma elasticum" (PXE) to describe a skin alteration observed 15 years earlier by his colleague D. Rigal. PXE is a rare autosomal recessive disorder resulting from mutations in the *ABCC6* gene. This disorder is characterized by progressive mineralization of both elastic and collagen fibers. Classic signs and symptoms include hypertension, reduced visual acuity, yellow cutaneous papules, and plaques due to cutaneous laxity, which are mainly localized to the neck, groin, armpits and flexural areas of arms and legs.[1,2] Diagnosis of PXE is difficult and time consuming for both the patient and the clinician.

In this report, we describe the case of a female who was diagnosed with PXE by biopsy of a palatal lesion, an uncommon site for this disease to be observed. A review of PXE-related oral mucosa lesions is also reported.

CASE REPORT

In February 2015, a 59-year-old female came to our Oral Medicine Service because of the presence of a white, asymptomatic palatal lesion. During the anamnesis, the patient reported a history of coronary artery disease and arterial hypertension, for which she was being treated with β-blockers and acetylsalicylic acid. In 2004, angioid streaks and choroidal neovascularization had been observed by using fluorescein and indocyanine green angiographies. At that time, the patient had also reported the appearance of multiple, small, yellow lesions on the skin of the antecubital fossa, the axillary and inguinal regions, and the neck. However, in April 2005, a biopsy of the cutaneous lesions located on the neck did not confirm the diagnosis of PXE. In 2010, the patient noted a progressive decrease in visual acuity, and optical coherence tomography detected alterations of the Bruch membrane–retinal pigment epithelium and changes in the thickness of the neuroepithelium in the macular region.

During the oral examination, two yellow-white macules on the soft palate (Figure 1A) and small confluent papules of the same color at the lower lip mucosa (Figure 1B) and on the floor of the mouth were observed. A skin examination revealed the presence of multiple, bilateral, yellow papules on the skin of the antecubital fossa (Figure 2A) and the loss of dermal elasticity on the neck and in the axillary and inguinal regions (Figure 2B).

With the patient's informed written consent, a tissue sample from the palatal lesion was collected by incisional biopsy and processed with hematoxylin and eosin stain (Figures 3A and 3B). Microscopy using orcein and von Kossa staining showed fragmented elastic fibers and intralesional calcium deposits, respectively (Figures 3C and 3D). On the basis of histopathologic, ophthalmologic, cardiovascular, and dermatologic data, the diagnosis of PXE was confirmed.

Our patient appeared in good general health, and since a definitive therapy for this genetic disorder is still not available, she was clinically managed with just a preventive approach, by means of specialist's follow-up visits, for early detection of ocular and cardiovascular diseases. Moreover, the patient did not perceive her skin lesions as unaesthetic, and refused any plastic dermatologic treatment.

DISCUSSION

Due to the multi-target nature of PXE, both the diagnosis and management of this disease require multiple clinical specialists, including dermatologists, ophthalmologists, pathologists, cardiologists, and oral medicine specialists. Asymptomatic skin manifestations, which are often the first clinical signs of PXE, usually occur between the first and second decades of the

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White sponge nevus: A condition not always clinically suspected

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Abstract

White sponge nevus (WSN) is an uncommon benign inherited disorder characterized by white and diffuse painless lesions in oral, esophageal, or genital mucosa. The lesions may develop at birth or later in childhood or adolescence, with careful clinical examination being sufficient for diagnosis in most cases. However, microscopic analysis may be necessary particularly in adults in which other whitish oral lesions may be clinically suspected. Dermatologists, dentists, and pathologists should consider WSN when evaluating multiple white oral lesions, thus preventing unnecessary treatments. Herein, we report four additional cases of WSN with emphasis on its clinical and histopathological features.

KEYWORDS
oral mucosa, white lesions, white sponge nevus

1 | INTRODUCTION

White sponge nevus (WSN) is a rare benign inherited disorder of autosomal-dominant transmission that involves mutations in the cytokeratin 4 and cytokeratin 13 genes, which result in keratin instability and tonofilament aggregation, causing whitish lesions on non-keratinized epithelial surfaces.[1-16] Familial cases may occur, but they are uncommon, as a result of irregular penetrance of the trait.[3,4,8,9]

Clinically, WSN appears as white or gray diffuse, thickened, corrugated or velvety painless plaques, which do not disappear upon stretching of the tissue, located especially on the oral mucosa.[5,6,15] The most commonly affected intraoral site is the buccal mucosa bilaterally, followed by lips, alveolar ridges, and the floor of the mouth.[2] Lesions may also appear on nasal, esophageal, rectal, or vaginal mucosae.[2,11] The whitish lesions of WSN usually develop during early childhood with no racial or gender predilection, presenting varied sizes and distribution, and may change over time.[5] WSN is a painless benign condition with no required treatment.[15]

The diagnosis of WSN is based on clinical findings and biopsy of mucosal lesions is usually unnecessary.[15] However, some adults may show oral manifestations of WSN clinically similar to other white lesions of oral mucosa, being necessary an oral biopsy followed by microscopical evaluation for proper diagnosis.[9] The microscopic features consist on oral hyperparakeratosis, acanthosis with intracellular edema, and eosinophilic deposition of tonofilaments of keratin around the nuclei of keratinocytes.[2,5,15] Few cases of WSN have been reported in the English language literature so far, mostly as single case reports

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Sporadic white sponge nevus caused by a mutation in the keratin 4 gene

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ABSTRACT

Herein, we present a sporadic case of white sponge nevus (WSN) on the cheek mucosa in a 27-year-old Japanese man. A definite diagnosis of WSN was obtained using the typical clinical appearance and microscopic features of the lesions. Histopathological and cytological studies should be conducted to differentiate this condition from other oral premalignant white lesions. A molecular mutation analysis revealed a missense mutation in exon 1A of the keratin 4 gene, which is correlated with the development of WSN. Hence, genetic analysis must be performed to obtain an accurate diagnosis in sporadic cases. The temporary regression of the lesion after treatment with oral amoxicillin hydrate (AMPC) 750 mg/day indicates that antibiotics are effective in symptomatic cases.

Introduction

White sponge nevus (WSN) is an inherited autosomal dominant disorder of the nonkeratinized oral mucosa. The condition is caused by defects in normal keratinization due to mutations in either the keratin type 4 (KRT4) or 13 (KRT13) gen [1]. Moreover, it is clinically characterized by the presence of white plaques in the tissues, which is referred to as nevus. These plaques appear predominantly as thick, velvety, spongy-like tissues on the bilateral cheek mucosa. The exact prevalence is not known. However, it affects less than 1 in 200,000 individuals worldwide without racial and gender predilection [2,3].

WSN is not commonly treated because the condition is benign without any potential risk for malignant transformation [1–3]. Therefore, an accurate diagnosis of the condition is important to prevent unnecessary treatments. Serious white lesions such as oral potentially malignant disorders (OPMDs), including leukoplakia and oral lichen planus (OLP), should be initially considered in the differential diagnosis with histopathological examination [4–8].

Herein, we present a sporadic (non-familial) case of WSN in a Japanese young adult. Moreover, the results of mutation analysis and response to antibiotic treatment were discussed.

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Case Report

Oral White Sponge Nevus: An Exceptional Differential Diagnosis in Childhood

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White sponge nevus is an autosomal dominant skin disorder characterized by white, irregular, diffuse plaques mainly affecting the oral mucosa. Histological findings of white sponge nevus are characteristic but not pathognomonic. We report a case of an oral white sponge nevus in a 6-year-old girl, which poses a problem in differential diagnosis with oral candidiasis. No treatment was performed because of the benign and asymptomatic nature of the lesions.

1. Background

White sponge nevus is a rare hereditary mucosal disorder characterized by asymptomatic spongy white plaques that affect oral mucosa and less frequently nasal, esophageal, rectal, and genial mucosa. Oral white sponge nevus appears as white or gray diffuse plaques thickened with multiple furrows and spongy texture located onbuccal, labial, gingival mucosa and floor of the mouth [1].

2. Case Report

A 6-year-old girl without any parental consanguinity, presented to our Department of Dermatology with chronic white lesions of oral mucosa that appear at the age of 2 years according to her mother. She was treated as mucosal candidiasis for more than 3 years without any result. There were no other family members affected by similar lesions. The lesions were asymptomatic except of some episodic burning sensations when eating acid or spicy food.

Cutaneous examination showed white irregular plaques with well-defined borders and symmetric distribution on the buccal mucosa (Figure 1). There was no associated erythema, and the plaques did not scrape off when using a tongue blade. There were no similar lesions elsewhere on the other mucosae. Histopathological examination showed superficial parakeratosis, acanthosis, and spongiosis with perinuclear eosinophilic condensation of epithelial cells. A minimal lymphocytic infiltration was present in the stroma. PAS coloration was negative. These features were characteristic of oral white sponge nevus. The genetic study was not performed.

Because of the benign and asymptomatic nature of the lesions, no medication was performed and the fungal treatment was stopped.

3. Discussion

White sponge nevus is an autosomal dominant genodermatosis that is often manifested in early childhood and showed no gender preference [2]. In our case, the lesions appear at the age of 2 years and were treated as oral candidiasis for many years.

The autosomal dominant characteristic of white sponge nevus shows irregular penetrance and variable expressivity in the same family. In our case, no similar lesions were found in parents or in siblings. The mutations concern the Keratin 4 or Keratin 13 genes, encoding mucosa-specific keratin intermediate filament proteins Keratin 4 and Keratin 13, "respectively," that are important for the assembly of keratin

BRIEF COMMUNICATION

A novel PTCH1 gene mutation in a pediatric patient associated multiple keratocystic odontogenic tumors of the jaws and Gorlin–Goltz syndrome

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ABSTRACT

Gorlin–Goltz syndrome (GGS) is an uncommon autosomal dominant inherited disorder which comprises the triad of basal cell carcinomas (BCCs), odontogenic keratocysts, and musculoskeletal malformations. Besides this triad, neurological, ophthalmic, endocrine, and genital manifestations are known to be variable. It is occasionally associated with aggressive BCC and internal malignancies. This report documents a case of GGS with a novel mutation in the PTCH1 gene in an 11-year-old child. The clinical, radiographic, histopathologic and molecular findings of this condition, and treatment are described, and a review of GGS was carried out.

KEY WORDS: Gorlin–Goltz syndrome, nevoid basal cell nevus syndrome, odontogenic keratocyst, pediatric, PTCH1 gene

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INTRODUCTION

Gorlin–Goltz syndrome (GGS) is inherited as an autosomal dominant trait with variable expressivity ranging from oral lesions to skeletal deformities.[1] The prevalence of GGS has been estimated to be 1:60,000 individuals.[2] It appears in all ethnic groups, but most often in whites;[3] it has a 3:1 male/female gender predilection.[4] The common manifestations in this syndrome include multiple basal cell carcinomas (BCCs), odontogenic keratocysts (OKCs) of the jaw, congenital skeletal anomalies, palmar pits, and intracranial ectopic calcifications of the falx cerebri. More than 100 less common features have been identified.[5] The molecular origin of the syndrome could be attributed to the loss of the human patched gene (PTCH1 gene) on chromosome 9q22.3–q31, which is a tumor suppressor gene.[6]

Despite the number of cases reported in the literature, the understanding of the complete form of GGS is not as yet conclusive. The present report and review attempt to highlight the salient features of an unusual case of multiple keratocysts in association with GGS with its management.

CASE REPORT

An 11-year-old boy was referred to our department with a chief complaint of swelling in the anterior region of the mandible of 2 weeks duration. Intraoral examination revealed displaced lower incisor teeth and swelling in the upper right canine region [Figure 1a-c]. The panoramic radiograph revealed three cystic lesions in each jaw. They were associated with an impacted right second molar, right canine, and left third molar in the maxilla. The lesions were located in the mandible and were related with an impacted left canine and lateral, left second and third molar and right third molar [Figure 1d].

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with metastatic disease and 47.6% in patients with the locally advanced form. The median duration of response in patients with metastatic disease was 7.6 months and in patients with locally advanced BCC was 9.5 months.[52]

Sonidegib, another inhibitor of SMO in the SHH pathway, has similar efficacy and is approved for locally advanced BCCs.[54] Unfortunately, as has been the case with several other such molecularly targeted anticancer drugs, about 30% of treated tumors either do not respond or develop resistance to treatment and relapse through mutations in SMO or a combination of SUFU inactivation and GLI2 amplification.[12,59] Mutations in SMO (the drug target) have been identified in 50% of resistant tumors; these mutations maintain Hedgehog signaling in the presence of SMO inhibitors.[60-62]

COURSE AND PROGNOSIS

With appropriate treatment, the prognosis for most patients with BCC is excellent. Control rates as high as 99% have been achieved by MMS. Although tumor control rates for primary tumors are high, patients must be monitored for recurrence and development of new primary BCCs. The risk for development of a second primary BCC ranges from 36% to 50%.[63] Periodic full-body skin examinations and counseling about sun protection are recommended for any patient with a history of BCC. This is especially important because patients with a history of BCC are at increased risk for melanoma. The prognosis for patients with recurrent BCC is favorable, although recurrent tumors are more likely to appear again and to behave aggressively. Patients with a history of recurrent disease must be monitored more frequently for the development of further recurrences and new primary tumors. An estimated 40% to 50% of patients with primary BCC will develop at least one or more further BCCs within 5 years.[2] For the rare patient with metastatic disease, the prognosis is poor, with a mean survival time of 8 to 10 months without treatment from the time of diagnosis. Recent clinical trials have highlighted a potential role of nicotinamide 500 mg twice a day[64] and of the nonsteroidal antiinflammatory drug celecoxib[65] in producing some decrease in BCC risk.

BASAL CELL NEVUS SYNDROME

- Patients with basal cell nevus syndrome (BCNS, Gorlin syndrome) inherit an inactivating mutation in the *PTCH1* gene.
- BCNS is a rare autosomal-dominant disorder with phenotypic abnormalities that include developmental anomalies and postnatal tumors, especially BCCs.
- In BCNS, the three most characteristic abnormalities are tumors such as medulloblastomas or BCCs, pits of the palms and soles, and odontogenic cysts of the jaw.
- Inhibitors of the Hedgehog signaling pathway (SMO inhibitors such as vismodegib, sonidegib) are FDA approved for advanced or metastatic BCCs.

Basal cell nevus syndrome, also known as *nevoid basal cell carcinoma syndrome* and *Gorlin syndrome* (Online Mendelian Inheritance in Man [OMIM] #109400), is a rare autosomal-dominant disorder associated with a panoply of phenotypic abnormalities that can be divided into developmental anomalies and postnatal tumors, especially BCCs.[66] Although individual aspects had been reported previously, their syndromic association was first appreciated widely in the late 1950s.[67,68]

EPIDEMIOLOGY

The prevalence of BCNS is variously estimated to be 1 in 31,000 to 1 in 60,000 persons.[69-71] The syndrome affects both sexes and occurs in a wide variety of cultural groups and therefore does not have a predilection for a particular skin type. The condition appears to have complete penetrance but variable expressivity of traits, such that their clinical presentation among families is nonuniform. Furthermore, as with many dominantly inherited conditions, new mutations are common. As a result, in many cases, patients may have no apparent affected ancestors or siblings.

ETIOLOGY AND PATHOGENESIS

GENETIC ABNORMALITY

Almost all known BCNS patients thus far carry mutations in the *PATCHED1* (*PTCH1*, UniGene Hs.494538) gene residing on the long arm of chromosome

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From the search for diagnosis to treatment uncertainties: challenges of care for rare genetic diseases in Brazil

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Abstract *Rare genetic diseases are an important public health problem, but they are still little studied in Collective Health. This article aims to analyze the 'therapeutic itineraries' of patients in search of a diagnosis and treatment for rare genetic diseases in the cities of Rio de Janeiro, Salvador and Porto Alegre. It focuses on the material challenges, emotional and structural problems faced in these trajectories. Semi-structured interviews were conducted with patients/caregivers and health professionals in the context of public health medical genetics. Our findings suggest that the experience of the rare genetic disease is aggravated by practical, inter-relational and bureaucratic/institutional problems. The reality of long and circuitous journeys to obtain a diagnosis, non-geneticists' lack of knowledge about rare diseases, difficulties in transportation and access to specialists, diagnostic and complementary examinations, and access to high-cost medicines and food supplies were common challenges in all the narratives examined in the three Brazilian cities. In addition, adherence to care provided by medical genetics requires action and strategies that depend on arrangements involving family members, physicians, patient associations, and the state.*

Key words *Rare disease, Genetics, Therapeutic itineraries*

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WORLD HEALTH ORGANIZATION

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Control of genetic diseases

Report by the Secretariat

1. Increased knowledge of genomics over the past two decades has made it apparent that the traditional category of *genetic diseases* represents only those conditions in which the genetic contribution is particularly marked, whereas in fact diseases can be arrayed along a spectrum representing the varied contribution of genes and the environment. The beneficial *applications* of genomic knowledge are still evolving, but it is expected that in the future genomics will have "a significant contribution to make to the area of public health".[1]

2. The interaction of genes with each other and with environmental factors underlies many aspects of human health and disease. However, this report focuses on the traditional category of *genetic diseases* and associated *congenital malformations*, both of which conditions are manifested early in life and for which clinical interventions are available. Genetic diseases are usually grouped into *single-gene disorders* (haemoglobinopathies, cystic fibrosis and haemophilia) and *chromosomal disorders* (Down syndrome, among others). These conditions are described as genetic diseases because a defect in one or more genes or chromosomes leads to a pathological condition. Multifactorial disorders, on the other hand, where genetic and environmental factors interact, have not traditionally been considered to be genetic diseases. Multifactorial disorders are usually categorized as *congenital malformations*, such as neural tube defect, cleft lip and palate, or *diseases with a genetic predisposition*, such as some chronic, noncommunicable diseases. In the literature, *congenital malformations* are often associated with *genetic diseases* because they both tend to present during pregnancy, at birth or in early childhood. Clinical genetics services provide care for people with both categories of disease, and registries of birth defects collect information about genetic diseases and congenital malformations. Because of their historical association, this report will consider both genetic disorders and congenital malformations.

3. Some genetic diseases, such as haemophilia, are carried on the X-chromosome (these X-linked disorders occur mainly in men). Others can arise from the presence of an abnormal gene in any autosome: if the gene is dominant, it results always in what is called a dominant condition, whereas if it is recessive many of these diseases appear only when the gene is inherited from both parents (and are thus called recessive conditions). For recessive conditions, the person who carries the abnormal gene on only one chromosome in the chromosomal pair may be unaffected or may even benefit; for instance, carriers of sickle-cell disease and thalassaemia genes may be protected from contracting malaria. This example demonstrates that environmental pressures can create reproductive advantages

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REVIEW ARTICLE

WILEY Reproductive Medicine and Biology

Mitochondrial replacement therapy and assisted reproductive technology: A paradigm shift toward treatment of genetic diseases in gametes or in early embryos

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Abstract

Background: Recent technological development allows nearly complete replacement of the cytoplasm of egg/embryo, eliminating the transmission of undesired defective mitochondria (mutated mitochondrial DNA: mtDNA) for patients with inherited mitochondrial diseases, which is called mitochondrial replacement therapy (MRT).

Methods: We review and summarize the mitochondrial biogenesis and mitochondrial diseases, the research milestones and future research agenda of MRT and also discuss MRT-derived potential application in common assisted reproductive technology (ART) treatment for subfertile patients.

Main findings: Emerging techniques, involving maternal spindle transfer (MST) and pronuclear transfer (PNT), have demonstrated in preventing carryover of the unbidden (mutated) mtDNA in egg or in early embryos. The House of Parliament in the United Kingdom passed regulations permitting the use of MST and PNT in 2015. Furthermore, the Human Fertilization and Embryology Authority (HFEA) to granted licenses world first use of those techniques in March 2017. However, recent evidence demonstrated gradual loss of donor mtDNA and reversal to the nuclear DNA-matched haplotype in MRT derivatives.

Conclusion: While further studies are needed to clarify mitochondrial biogenesis responsible for reversion, ruling in United Kingdom may shift the current worldwide consensus that prohibits gene modification in human gametes or embryos, toward allowing the correction of altered genes in germline.

KEYWORDS
germ line gene therapy, maternal spindle transfer (MST), mitochondrial bottleneck effect, mitochondrial diseases, mitochondrial replacement therapy (MRT)

1 | INTRODUCTION

In the recent era, many of pathogenic (causative) mutations associated with disease or disorders have been found due to the progress of the Human Genome Project (HGP). Mutation can be found both in the nuclear DNA (nDNA) and in the mitochondria DNA (mtDNA), and if pathogenic (causative) mutations exist in germ line, that is, present in the sperm or oocyte, they would be inherited by the offspring, and sometimes, even passed on to future generations. The patient who harbors pathogenic mutations that can cause progressive and lethal diseases with no available cure is often required to make difficult reproductive choices. In order to have a healthy baby,

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REVIEW

Splicing modulation therapy in the treatment of genetic diseases

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Abstract: Antisense-mediated splicing modulation is a tool that can be exploited in several ways to provide a potential therapy for rare genetic diseases. This approach is currently being tested in clinical trials for Duchenne muscular dystrophy and spinal muscular atrophy. The present review outlines the versatility of the approach to correct cryptic splicing, modulate alternative splicing, restore the open reading frame, and induce protein knockdown, providing examples of each. Finally, we outline a possible path forward toward the clinical application of this approach for a wide variety of inherited rare diseases.

Keywords: splicing, therapy, antisense oligonucleotides, cryptic splicing, alternative splicing

Introduction

Genetic diseases are generally rare diseases caused by mutations in specific genes. Sometimes mutations in different genes can give rise to similar phenotypes, eg, there have been dozens of genes identified in patients suffering from muscular dystrophies.[1] However, mutations in a single gene can also give rise to multiple diseases with varying phenotypes. Probably the most notorious example is the *LMNA* gene, in which mutations are associated with multiple phenotypes, including Emery–Dreifuss muscular dystrophy, familial partial lipodystrophy, limb girdle muscular dystrophy, dilated cardiomyopathy, Charcot–Marie–Tooth disease, restrictive dermopathy, and Hutchinson–Gilford progeria syndrome (HGPS).[2] For a significant number of patients with, or suspected of having a genetic disease, the mutation in the causative gene has not yet been identified. However, with the rapid advances made by "next generation sequencing", it is anticipated that mutations will soon be identified for almost all patients with genetic disorders; the International Rare Disease Research Consortium (IRDiRC) has set itself an ambitious goal of having the means available to diagnose most rare genetic diseases by 2020 (http://www.irdirc.org).

With the availability of next generation sequencing, it is now possible to perform a more in-depth analysis of candidate genes. In the past, generally only exons and the donor and acceptor splice sites (ie, the first and last two base pairs of an intron, respectively) were analyzed. However, it is now feasible to analyze complete introns and there are multiple publications that report deep intronic mutations that activate cryptic splice sites and thus disrupt normal transcript processing.[3] In parallel, antisense-mediated splicing modulation has been developed from preclinical cell and animal models into the clinical trial phase for Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA).[4–6] This approach makes use of antisense oligonucleotides (ASOs, small

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