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Clinical, etiological and therapeutic aspects of Dyskeratosis Congenita

Aspectos clínicos, etiológicos y terapéuticos de la disqueratosis congénita

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Abstract

The Dyskeratosis congenita corresponds to the first genetic entity described among telomeropathies, whose classic form is characterized by presenting the mucocutaneous triad of reticulated skin-lace pigmentation, nail dystrophy and oral leukoplakia. It can also occur with bone marrow failure, hematological and solid tumors, corresponding to the most serious complications. In addition to immunodeficiencies, dental, lung and liver disorders and other aspects considered minor. In turn, it presents varied genetic locus heterogeneity, with at least 14 genes involved in the telomere´s shortening, therefore associated with dyskeratosis congenita or similar phenotypes. This review discusses in addition to the clinical characteristics, the various etiological causes, evolution, available therapeutic options, and the differential diagnostic of this entity in order to provide an interdisciplinary and individualized medical evaluation that includes adequate genetic counseling.

Keywords: dyskeratosis congenita, telomeropathies, clinic, etiology, treatment.

Resumen

La disqueratosis congénita corresponde la primera entidad genética descrita entre las telomeropatías, cuya forma clásica se caracteriza por presentar la tríada mucocutánea de pigmentación reticulada de encaje en piel, distrofia ungueal y leucoplasia oral. Puede cursar además con insuficiencia de la médula ósea, tumores hematológicos y sólidos que corresponde las complicaciones más graves. Además de inmunodeficiencias, alteraciones dentales, pulmonares y hepáticas y otros aspectos considerados menores. Presenta a su vez una variada heterogeneidad genética de locus, con al menos 14 genes implicados en el acortamiento de los telómeros, asociados por lo tanto a la disqueratosis congénita o a fenotipos similares. Esta revisión discute además de las características clínicas, las diversas causas etiológicas, evolución, opciones terapéuticas disponibles y diagnóstico diferenciales de esta entidad con el objeto de brindar una evaluación médica interdisciplinaria e individualizada que incluya un adecuado asesoramiento genético.

Palabras clave: disqueratosis congénita, telomeropatías, clínica, etiología, tratamiento.

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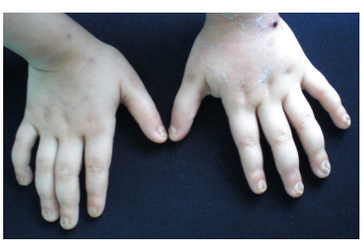
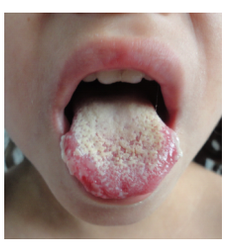
Introduction

The disorders in the telomeres´ biology called telomeropathies represent a group of genetic entities, in which dyskeratosis congenita (DC) was the first to be described (1), whose classic form is clinically characterized by presenting the diagnostic mucocutaneous triad of Reticulated skin lace pigmentation (1,2), mainly affecting the neck area and the upper anterior thorax (2), nail dystrophy and oral leukoplakia (1-10) (Fig. 1).

Figure1. Nail dystrophy and oral leukoplakia.





The typical dermatological manifestations occur in the first years of life, however, the presentation can be heterogeneous (8,9). The aforementioned nail dystrophy first affects the fingernails, begins with grooves and longitudinal divisions, which progresses resulting in rudimentary, small or absent nails. For its part, the leukoplakia affects the oral mucosa, tongue and oropharynx, and treatment is symptomatic. Approximately the 30% present malignant transformation to squamous cell carcinoma (4), so they require frequent follow-up with early biopsy in suspected areas (4,8).

Posteriorly, it was shown to be associated with bone marrow failure (1-5), with cytopenia of one or more hematopoietic cell lineages, and the most serious complication corresponded (1). It can affect up to 80-90% of cases at the age of 30 years and its sequelae represent more than 70% of deaths in patients with this entity (8). The presence of the mucocutaneous

triad can help differentiate the DC from other types of bone marrow failure (10). It also presents with immunodeficiencies, predisposition to present dental caries, hypodontia, bleeding, recession and bone loss that simulate juvenile periodontitis, taurodontism, gingival inflammation and brown intraoral pigmentation (1,2,4,6,8,10). The evidence of multiple permanent teeth with decreased root / crown ratio may suggest the diagnostic of the DC (4). Other clinical findings include pulmonary fibrosis, and liver failure or fibrosis (1-3,5,7,10). They also have a 50-fold increased risk of developing hematologic and solid tumors, including myelodysplastic syndrome, acute myeloid leukemia, non-Hodgkin lymphoma, the squamous cell carcinoma of the head and neck, the esophageal cancer, anogenital cancer and basal cell carcinoma, as serious complications (1,2,4,5,8,10).

The squamous cell carcinoma of the head and neck is the most frequent solid tumor in patients with DC, with a mean age of onset of 32 years, compared to 67 years in the general population.

The recognition includes additional minor features such as intrauterine growth retardation, developmental delay and microcephaly, the signs of premature aging, premature graying of hair, excessive sweating, and short stature (4.7-10). Among the ocular abnormalities are described nasolacrimal duct stenosis, epiphora, blepharitis, few eyelashes, ectropion, entropion, and trichiasis (2-4,10). On the other hand, the retinal changes are rare and include the bleeding, infarction of the nerve fiber layer, arteriosclerosis, macular edema, preretinal fibrosis, and optic atrophy (4). Furthermore, cardiomyopathy, enteropathy with malabsorption, esophageal and urethral stenosis, hypogonadism, testicular atrophy, osteoporosis, and avascular necrosis of the shoulder and hip joints can be seen (2-4,7,10). These clinical manifestations affect patients in different ways and with a variable percentage (4). The DC often goes unnoticed due to the late onset of mucocutaneous findings and in some cases may not occur. The broad spectrum of clinical presentation and the lack of conclusive laboratory evidence can sometimes make clinical diagnostic challenging (1).

In the DC like other telomere diseases, the symptoms are associated with the degree of telomere´s shortening, caused by mutation in the telomerase genes. In the most severe cases and with the telomere shortening less than the 1% percentile of the population, the disease appears in the first 10 years of life or even during the prenatal stage. In the cases of less severe telomeric shortening, the disease appears at an age between 15 and 25 years, in these cases it is below the 10% percentile of the population and can appear as spinal aplasia or pulmonary fibrosis and whose probability is associated with the gene mutated. The genetic diagnostic is essential due to the limited efficacy of therapeutic options, and the common genetic anticipation in DC makes genetic counseling a priority (1).

Incidence

The DC has an estimated annual incidence of less than 1 in 1,000,000 (4), it was first described by Zinsser in 1906, in male patients with the aforementioned mucocutaneous triad (3,4,6). It was recognized as a clinical entity by Engman in 1926 and Cole in 1930, and is known as the Zinsser-Cole-Engman syndrome, which will be discussed later (4). In 1963, the first female case was documented (3).

Etiopathogenesis and diagnostic

The telomeres are made up of 6 nucleotide repeats at the ends of chromosomes (5). It is a nucleoprotein complex essential for chromosomal stability, and they shorten with each cell division (5,7). The regulation of the telomere´s length is implicated in cell aging and tumorigenesis (6). Therefore, mutations in the key genes of the telomere maintenance machinery are related to entities such as the DC, which can cause bone marrow failure and cancer (6,7,9,10).

This knowledge allowed the development of a diagnostic test through flow cytometry with fluorescent in situ with hybridization in leukocyte subsets. The size of the telomeres in leukocytes less than the first percentile for age is more than 95% sensitive and specific in patients with the DC (3,5,7). In addition to intervening in the diagnostic, the study of telomeres has greatly contributed to discovering the genetic causes of the DC (3).

At least 14 genes involved in the telomere´s shortening, associated with DC or similar phenotypes have been identified (Table 1), and represent between 70 to 80% of patients with this disorder (3,5,7). They exhibit various patterns of inheritance, including that linked to the recessive X chromosome (OMIM # 305000) (1,3-5), due to the pathogenic variants

in the dyskerin 1 (DKC1) gene, which encodes a pseudouridine synthase, and whose gene is It is located in Xq28, among the most common and classic of the DC, as well as autosomal dominant (OMIM # 127550) and / or recessive (OMIM # 224230) (1-6,8,9) patterns. However, between 20 to 40% of cases, genetic causes are undetectable (2,4).

Table 1. Etiopathogenesis in the alteration of the telomere biology associated with the DC (3,5,7-9).

Mechanism of action	Gene	Genetic Inheritance Pattern
Telomerase holoenzyme complex	*DKC1**	LX
	*TERC**	AD
	*TERT**	AD o AR
	*NOP10**	AR
	*NHP2**	AR
Telomere´s Protection Complex	*ACD*	AD o AR
	*TINF2**	AD
	POT1	AD
Proteins that limit the telomeres	*CTC1*	AR
	STN1	AR
Other proteins that directly or indirectly interact with key cellular processes	*RTEL1*	AD o AR
	NAF1	-
	WRAP53	AR
	PARN	AR

* Implicated in the regulation in the telomere´s length (9)
AD: autosomal dominant.
AR: autosomal recessive.
XL: X-linked recessive chromosome.

The DC associated with the X chromosome occurs in the male sex. It manifests clinically between 5 to 12 years, it can present a variable age of onset, symptoms and severity, even in individuals with the same mutation. In this pattern of inheritance, the women may exhibit less severe clinical features until more advanced ages (4). The DKC1 gene has a highly conserved sequence that binds to small nucleolar RNAs, it is responsible for the biogenesis of ribosomes and is part of the telomerase complex when it binds to telomerase RNA or TERC (2,9). The Mitchell and Collins studies were the first to show a connection between the telomeres and human disease through the aberrant function of dyskerin and the shortening of the telomeres (3). Therefore, the germline mutations in genes involved in the telomere´s biology result in abnormal shortening of these structures for age, resulting in chromosomal instability and the progressive cell death (2).

Therefore, it is a disease with a defective maintenance of the telomeres, which leads to a premature shortening, to a replicative senescence, to a premature exhaustion of the stem cells and the failure in different tissues, and it manifests itself mainly in the highly proliferating of the mucocutaneous tissues (1,4, 10). However, the mutations in the telomerase and the telomere´s components have also been identified in patients with aplastic anemia, pulmonary fibrosis and liver disease (4).

Additionally, the genotype-phenotype correlation is very complex due to various factors, to including a variety of underlying hypomorphic gene mutations, to the disease anticipation, as well as genetic and environmental modifying effects (4).

Treatment

There is not curative therapy for the DC, and the patients generally die prematurely from bone marrow failure, due to the poor hematopoietic stem cell turnover, so an option is the allogeneic transplantation, which may be associated with complications. Furthermore, the follow-up is crucial in the presence of tumors or serious infection by opportunistic agents, among the main causes of death between the second and the third decades of the life (2,4,5,11).

The treatment of the squamous cell carcinoma of the head and the neck may involve surgical treatment, radiation, and chemotherapy, while avoiding the exposure to potential carcinogens such as ultraviolet radiation, alcohol, and tobacco (8).

The use of low doses of systemic retinoids has shown some improvement in the skin and the nails, but the secondary effects and the long-term effectivity are uncertain (11). Furthermore, it has been described that up to 70% of the patients with the CD and severe bone marrow failure may temporarily benefit from therapy with androgens or androgen derivatives, but there is no cure for the disease (8, eleven). The biological mechanisms by which these compounds effectively treat the

bone marrow failure are still unknown. However, it has been proposed that the androgens can directly increase the erythropoietin production or act on the erythropoietin receptor to generate a hematological response. A limited number of studies on human´s cell lines and mouse models with aplastic anemia suggest that the androgens can increase telomerase expression and telomere´s length (8).

Other exogenous therapies can correct the telomerase´s defect and improve the cell growth, as well as the use of the modulators involved in the maintenance of the telomeres, have been suggested as new therapeutics methods (11). Among them, the expression of a dysquerin-derived peptide, a genetic suppressor element 24.2 (GSE24.2), which increases the telomerase activity, reduces the pathogenic effects of Dkc1 mutations, decreases the DNA damage and the oxidative stress, thus suggesting a new therapeutic approach. Likewise, the expression of the GSE4 activates the c-myc and TERT promoters, in addition to increasing the expression of c-myc, TERT and TERC (12-14).

Additionally, the activation of the telomerase through the use of vectors in genetic therapy of adeno-associated viruses that carry the telomerase´s Tert gene in mouse models independent of aplastic anemia due to short telomeres showed that a high dose of this vector was targeted at the bone marrow compartment level, including the hematopoietic stem cells, that improve substantially the survival, it results in a significant increase in the telomere length in the peripheral blood and in the bone marrow cells, as well as a better blood count. These findings indicate that the telomerase genetic therapy represents a novel therapeutic strategy to treat the aplastic anemia caused or associated with short telomeres (9,15).

The integration of an interdisciplinary team is independent in each case, but will generally include to Dermatology, Otorhinolaryngology, Dentistry, Maxillofacial Surgery, Oncology, Gynecology (8), Medical Genetics and include early genetic tests to carry out timely genetic counseling (8,11).

Evolution of the DC

During the follow-up of the disease when the mucocutaneous triad occurs, the bone marrow failure usually appears. However, sometimes the manifestation of the disease is ambiguous. The aplastic anemia occurs at a mean age of presentation of 11 years, it is macrocytic, with high levels of fetal hemoglobin. It begins with thrombocytopenia and during the evolution, it becomes general and severe bone marrow failure develops. The premature mortality can occur in up to 80% of cases from opportunistic infections. Besides, they can progress in different ways with the appearance of the myelodysplasia in one or more lineages (4).

There is an excessive shortening of the telomere that can lead to genomic instability. The Electronic Microscopy studies revealed that the cells in the DC have an immature embryonic nucleus and a predisposition to undergo a malignant transformation. Besides, the epithelial barrier is less effective than in the normal epithelium, so there is a greater permeability of the harmful and carcinogenic substances in the germ layers. Therefore, an increase in the rate of malignant transformation is observed in the leukoplastic areas, requiring the periodic monitoring. In addition, they have a cumulative incidence of the risk of malignancy of 40 to 50% at 50 years, for example, they can develop Hodgkin´s lymphoma, laryngeal and bronchial carcinoma, adenocarcinoma of the gastrointestinal tract, among others at the skeletal and genitourinary level (4).

Clinical variations

The Zinsser-Engman-Cole syndrome (OMIM #305000) is the most severe variant and is characterized by the progressive marrow failure, intrauterine growth retardation, developmental delay, microcephaly, cerebellar hypoplasia, mental retardation, progressive immunodeficiency and the mucocutaneous triad, which usually leads to death in the early childhood (1,4,6,8,10,11,16). It is due to the mutations in the DKC1 and RTEL1 genes, mainly due to the decreased telomerase´s activity. The diagnostic can be made if you have four or more of these findings, or if you have cerebellar hypoplasia and additional features of the DC (4).

The Revesz syndrome (OMIM #268130) was first described in 1992, it is due to the mutations in the TINF2 gene, it is another infrequent variant of the DC, the defining characteristic is the bilateral exudative retinopathy, which occurs in most cases in association with the intracranial calcification and the alterations more associated to the DC disorders, as the bone marrow failure and the mucocutaneous

abnormalities; In addition, it may present intrauterine growth retardation, cerebellar hypoplasia, and developmental delay (4,6,11,17).

The Coats Plus syndrome (OMIM #612199) is an infrequent disorder with an autosomal recessive pattern of inheritance, due to the nonsense mutations in the CTC1 gene, characterized by the cerebroretinal microangiopathy, with intracranial calcifications, osteopenia, and gastrointestinal bleeding (4,18,19).

Differential diagnostic

The Naegeli-Franceschetti-Jadassohn syndrome (OMIM #161000), is differentiated by the lack of the leukoplakia, the bone marrow failure and an increased risk of malignancy (11). However, this and the reticular pigmentary dermatopathy (OMIM # 125595), allelic alterations, can have a similar reticulated hyperpigmentation (20,21).

On the other hand, the Fanconi anemia (OMIM # 227650) generally presents diffuse or uniform pigmentary abnormalities, and the pancytopenia has an earlier onset compared to the DC (11,16). It also presents eyes, kidney and limbs abnormalities (16). As well as other chromosome reorganization and break syndromes such as the Bloom syndrome (OMIM # 210900) 16,22, the Nijmegen break syndrome (OMIM # 251260), the Seckel syndrome (OMIM # 210600), and finally the pseudo-TORCH syndrome, due to the brain calcifications (22).

Other entities include the Rothmund-Thomson syndrome (OMIM # 268400), and the simple epidermolysis bullosa (OMIM # 131900), both of which have mottled pigmentation with similar poikiloderma (18,20). In addition, the Kindler's syndrome (OMIM # 173650), and the poikiloderma with Clericuzio-type neutropenia (OMIM # 604173) (16,23,24). In the Bloom, Kindler and Rothmund-Thomson syndromes, the skin lesions may be similar to those seen in the DC, but are more sensitive to the sun and differ in associated characteristics (16). Finally, the patients with graft-versus-host disease have poikiloderma, lichen planus-like changes in the mucosa, and obvious nail dystrophy after the bone marrow transplantation (16,20).

Conclusions

A wide range of genetic alterations generates a wide spectrum of clinical manifestations with variable age of onset, this fact make challenging the diagnostic in this disorder of telomere´s biology. Therefore, the DC is a hereditary, clinical and genetically heterogeneous syndrome of the bone marrow failure and a prototype of this type of disorder. For this reason, the medical evaluation must be interdisciplinary and individualized, offering the available therapeutic options and timely genetic counseling based on genetic diagnostic and the telomeric length studies.

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