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Dyskeratosis Congenita – Diagnostic Significance

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Abstract

Dyskeratosis congenita is an inherited genetic multisystem skin condition characterized by darkening of skin, progressive nail dystrophy, mucosal leukoplakia and bone marrow failure.

Keywords: Dyskeratosis congenita, Leukoplakia, Nail dystrophy, Aplastic anemia

Introduction

Dyskeratosis congenita is a rare multisystem disorder characterized by mucocutaneous triad of abnormal skin pigmentation, nail dystrophy, mucosal leukoplakia and bone marrow failure. It exhibits considerable clinical and genetic heterogeneity. A variety of other abnormalities like dental, gastrointestinal genitourinary, immunological, neurological, ophthalmic, pulmonary, skeletal and hair graying/ loss have been reported.

Skin shows reticulate hyperpigmentation affecting the flexures, particularly neck, axillae and inner upper thighs. Progressive nail dystrophy present with longitudinal ridging and raised irregular free edges. Leukoplakia may be present at any mucosal site. The oral mucosa is most frequently affected followed by mucosa of urethra, glans penis, vagina and rectum. Patients who develop bone marrow abnormalities (aplastic anaemia) are at a risk of life threatening infections and bleeding.

Discussion

Dyskeratosis congenita is an inherited genetic skin condition characterized by darkening of skin, progressive nail dystrophy, mucosal leukoplakia and bone marrow failure.[1,2,3,4,6,15,16] The prevalence is estimated as one case per million population.

Synonyms

- Dyskeratosis congenita, X linked
- Dyskeratosis congenita, scoggins type
- Dyskeratosis congenita, autosomal dominant
- Dyskeratosis congenita, autosomal recessive
- Hoyeraal – Hreidarsson syndrome
- Zinsser – Cole – Engman syndrome

Dyskeratosis congenita is genetically heterogeneous, mainly inherited as X-linked recessive pattern however autosomal dominant and recessive forms are also recognized. It is caused by a mutated gene, DKC 1 located in the X chromosome and another gene TERC; both encode the components of the telomerase complex.[1,14,18]

The gene (DKC I) was identified in 1998 and gene (TERC – RNA component of telomerase) in 2001. Mutation in the TERC genes and in the TERT gene, gene for telomerase reverse transcriptase, has been identified in patients with aplastic anaemia.[5,14,17] DKC I is expressed in all tissues of the body, indicating that it has a vital "house – keeping function" in the human cell. DKC I gene located in the Xq 28 which encodes the protein, dyskerin.[3,18,24] Dyskerin composed of 514 aminoacids. It has a role in the ribosomal RNA processing by pseudouridilation of specific reduces of rRNA. Dyskerin also associates with the RNA component of telomerase (hTR).[18,19,24,25,30] Telomerase is an enzyme complex, which is important in the maintenance of the ends (telomeres) of chromosomes.[30,31,32] Telomerase are shorter in cells from patients with autosomal form of Dyskeratosis congenita. This suggests that the disease might be caused by disturbed telomerase activity.[11,12,13,14,17,18,23]

If male inherits the DKC I genetic defect as single X chromosome, he will have the disease and female would need to inherit two defective chromosomes in order to have the disorder. Because of this inheritance pattern, male predominance is observed with ratio of 10:1.

Clinical manifestations of Dyskeratosis congenita appear during childhood. The skin pigmentation and nail changes typically appear first, usually by the age between 5-15 years. The more serious complications of bone marrow failure develop in the second and third decade of life.[5,20,22,26,30,32]

The primary cutaneous finding is abnormal skin pigmentation with tan – to gray hyperpigmented or hypopigmented macules and patches in a mottled or reticulated pattern. During the first decade of life, patients develop poikiloderma of sun exposed areas and occasionally bullae. The cutaneous presentation may clinically and histologically resemble graft versus host disease. The typical distribution involves the sun –

exposed areas including upper trunk, neck and face.[4,6,16,20,32] Other cutaneous features are alopecia of scalp, eyebrows and eye lashes; pre-mature graying of hair, hyperhidrosis, hyperkeratosis of palms and soles and loss of dermal ridges on finger and toes (Adermatographia).

The nail dystrophy is seen in approximately 90% of patients. The nail changes are first observed at approximately at the age of 2 to 5 years; fingernail involvement often proceeding toenail involvement. The Progressive changes begins with ridging and longitudinal splitting, atrophy thinning and distortion eventuate in small, rudimentary or absent nails.[4,28,29,32]

Approximately 80% of patients are affected by mucosal leukoplakias. It typically involves buccal mucosa, tongue and oropharynx. Other mucosal surfaces like urethra, glans penis, vagina, rectum, oesophagus involved and subsequent constriction and stenosis can occur at these sites.[20,22,32]

There is an increased incidence of neoplasia particularly squamous cell carcinoma of the mouth, rectum, cervix, vagina, esophagus and skin. These neoplasms may occur in the third or fourth decades with in the sites of leukoplakia. Other malignancies reported include Hodgkin lymphoma, adenocarcinoma of gastrointestinal tract, and bronchial and laryngeal carcinomas.[27]

Pulmonary complications include fibrosis and abnormalities of vasculature. Patients with Dyskeratosis Congenita should avoid drugs which produce pulmonary toxicity. Some patients may also have learning difficulties and mental retardation. Dyskeratosis Congenita may be associated with conjunctivitis, blepharitides and lacrimal duct stenosis resulting in epiphora.

The more serious complication of bone marrow failure (aplastic anemia) develops in the 2nd and 3rd decade of life. Primary refractory pancytopenia, bone marrow hyperplasia and megaloblastosis, eventuating in severe hypoplasia of marrow are often noticed. Leucopenia and thrombocytopenia may also be present, resulting in hematological picture similar to Fanconi's Anemia.[5,9,10,12,21,24] Bone marrow failure is the principal cause of early mortality with an additional pre-disposition to malignancy and fatal pulmonary complications.

Diagnosis based on clinical criteria alone is difficult and unreliable, especially where non-cutaneous abnormalities precede classical mucocutaneous features. Prenatal DNA testing is a useful diagnostic aid in the detection of the genes responsible in Dyskeratosis Congenita.[9,13,14,17,19] Immune function studies shows defects in immunoglobulin levels and in cell mediated immunity. Chromosome abnormalities have been found in fibroblasts, bone marrow cells and lymphocytes.[2,12,21,23] Elevated von Willebrand factor levels have been associated with fatal vascular complications after bone marrow transplant and may be a marker for patients with a pre disposition for endothelial deterioration. Mutational analysis may be useful in confirming the diagnosis. Imaging studies show calcification of basal ganglia. Biopsy is recommended for skin lesions. Oral leukoplakic lesions shows non-specific hyperparakeratosis or hyperorthokeratosis and acanthosis.

The goals of pharmacotherapy are to reduce morbidity and to prevent complications. Short term option for bone marrow failure includes anabolic steroids like oxymetholone, granulocyte macrophage colony – stimulating factor, granulocyte colony stimulating factor and erythropoietin. Erythropoietin (Epogen, 50-100 U/kg IV/SC 3times/week) stimulates division and differentiation of erythroid progenitor cells Filgrastim (Neupogen, 5 mcg/kg/d SC) activates and stimulates production, maturation, migration and cytotoxicity of neutrophils.[18]

The long term curative option is hemopoietic stem cell transplantation (SCT). The success rate of SCT is limited because of a high prevalence of fatal pulmonary complications. Early diagnosis of Dyskeratosis congenita through genetic analysis may also help identify patients. This helps in early harvest and storage of their bone marrow for use after anticipated bone marrow failure.

70% of patients with Dyskeratosis congenita die either directly from bone marrow failure or its complications. Other cause of mortality arises from sudden pulmonary complications and pulmonary disease. Fatal opportunistic infections like pneumocystis carinii pneumonia and cytomegalovirus infection have been reported.

Conclusion

Dyskeratosis congenita is an inherited condition characterized by many abnormalities including abnormal skin pigmentation and nail dystrophy, premature ageing and an increased risk of malignancy, particularly of skin and gut. The most common feature of disease is bone marrow failure (aplastic anemia). The diagnosis of Dyskeratosis congenita – although it is a rare disease – should be considered in every child first seen with aplastic anemia or thrombocytopenia. It is of concern to the dentist due to the high incidence of Oral Leukoplakia and its subsequent malignant transformation.

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