REVIEW ARTICLE

Dyskeratosis Congenita

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Introduction

Dyskeratosis congenita (DKC) is a rare inherited bone marrow failure and cancer predisposition syndrome with prominent mucocutaneous abnormalities and features of premature aging with a prevalence of 1 in 1 million people (1,2). It is characterised by mucocutaneous triad of abnormal skin pigmentation, dystrophy of nails and mucosal leukoplakia and pigmentation (2). It is caused by defects in telomere biology due to defective telomerase function (1, 3, 4). X-linked recessive, autosomal dominant and autosomal recessive forms of the disease are recognised (2). Dyskeratosis congenita affects all systems of body (3). Bone marrow failure is the principal cause of early mortality with an additional predisposition to malignancy and fatal pulmonary complication (2).

History

The name, dyskeratosis congenita (DKC), was derived after the description by Zinsser, in 1910, of two brothers who had nail dystrophy, oral leukoplakia, and skin pigmentation and later by Engman and Cole leading to the designation Zinsser-Engman-Cole syndrome (5). Early reports focused on the dermatologic findings. As more cases were described with other medical complications, it became clear that DKC is a complex, multisystem disorder (5, 6). More than 500 cases have been reported in the literature (7).

Genetics and Pathogenesis

DKC is a genetically heterogeneous, with X-linked recessive, autosomal dominant and autosomal recessive subtypes. DKC is related to telomerase dysfunction (4, 8).To date, mutations in six genes of telomerase and telomere components have been identified in patients with DKC (9). All genes associated with this syndrome (i.e. DKC1, TERT, TERC, and NOP10) encode proteins for the telomerase complex (3, 10, 11). Telomeres are repeat structures found at the end of chromosomes that function to stabilize chromosomes, they have critical role in preventing cellular senescence and cancer progression. With each round of cell division, the length of telomeres is shortened and the enzyme telomerase compensates by maintaining telomeres length in germ-line and stem cells. Rapidly proliferating tissues with the greatest need for telomere maintenance (e.g., haematological and dermatological system) are at greatest risk of failure (12). In the X-linked form, the defect lies in the DKC1 gene located at Xq28, which encodes for protein Dyskerin which has a role in ribosomal RNA processing and telomere maintenance (13). In the autosomal dominant form, mutation in the RNA component of telomerase (TERC) or telomerase reverse transcriptase (TERT) are responsible for the disease phenotype (14). Defect in the NOP10 gene were found in association with autosomal recessive form (15). Patients with DKC have reduced telomerase activity and abnormally short tracts of telomeric DNA as compared with normal controls.

Clinical Features

The triad of reticular hyper-pigmentation of the skin, nail dystrophy, and leukoplakia are the characteristics DKC. Patient, usually present during first decade of life, with the skin hyper-pigmentation and nail changes typically appeared first. The mucocutaneous features typically develop between ages of 5 and 15 years. Male to female ratio is approximately 13:1 (3).

Clinical findings in dyskeratosis congenita include abnormal skin pigmentation (90%) in form of lacy, reticular pigmentation, primarily of the neck and chest; may be subtle or diffuse hyper- or hypopigmentation (2, 3). Nail dystrophy occur in 88% cases in form of abnormal fingernails and toe nails, may be subtle, with ridging, flaking, or poor growth, or more diffuse with nearly complete loss of nails. Finger nails involvement often preceding toe nail involvement. Mucosal involvement occurs in around 80% cases. Leukoplakia typically involves oral mucosa, tongue and oropharynx. Early greying of hairs or hair loss (16%) and hyperhidrosis (15.3%) also seen in DKC. Other mucosal sites may be involved (e.g. oesophagus, urethral meatus, glans penis, lacrimal duct, conjunctiva, vagina, and anus). Constriction and stenosis at these sites leads to dysphgia, dysuria, phimosis, and epiphora. Ophthalmic manifestations reported in 80% patients in form of epiphora (30%) due to stenosis of the lacrimal drainage system, blepharitis, sparse eyelashes, ectropion, entropion, trichiasis, and

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exudative retinopathy (Revesz syndrome). Dental involvement occurs in form of dental caries (17%), periodontal disease, decreased root/crown ratio, taurodontism (enlarged pulp chambers of the teeth). Cardiovascular involvement is rarely reported, include atrial or ventricular septal defects, and dilatated cardiomyopathy (3). Pulmonary fibrosis and pulmonary vascular abnormalities seen in 20% cases. Gastrointestinal finding include oesophageal stenosis/webs (17%), enteropathy, hepatosplenomegaly and liver fibrosis and cirrhosis. Genitourinary involvement in form of urethral stenosis (5%), hypospadias, and hypoplastic testes. Musculoskeletal problems include osteoporosis (5%), avascular necrosis of the hips and shoulders, scoliosis, and mandibular hypoplasia. Neurologic involvement occur as developmental delay, mental retardation (25%), microcephaly (5.9%), cerebellar hypoplasia (Hoyeraal-Hreidarsson syndrome), intracranial calcifications (Revesz syndrome), learning disabilities, ataxia (6.8%), deafness (0.8%), and schizophrenia (two case reports). Hypogonadism/undescended testes (5.9%), short stature (19.5%), intrauterine growth retardation (7.6%), and developmental delay also reported with DKC.

Bone marrow failure (BMF) occurs in 85-90% of patients. It is major cause of death with approximately 70% of deaths related to bleeding and opportunistic infections. There is increased risk of malignancy (8.8%) especially malignant mucosal neoplasms like squamous cell carcinoma (SCC) of mouth, nasopharynx, oesophagus, rectum, vagina or cervix. These often occur at sites of leukoplakia. The prevalence of SCC of skin is also increased. Other malignancies reported include Hodgkin lymphoma, adenocarcinoma of GIT, myelodysplasia and bronchial and laryngeal carcinoma (7). Malignancies tend to develop in third decade of life.

Differential Diagnosis

The differential diagnosis of DKC includes fanconi's anaemia, pachyonychia congenital, and white spongy nevus (16). DKC should be differentiated from Fanconi's anaemia because aplastic anaemia and cutaneous pigmentation occur in both. Fanconi's anaemia may have a possible association with oral squamous cell carcinoma (17). In contrast to Dyskeratosis congenita, Fanconi's anaemia is an autosomal dominant condition with concomitant skeletal and renal abnormalities. But there is no nail dystrophy or oral leukoplakia in Fanconi's anaemia. Pachyonychia congenita is an autosomal dominant disease characterized by mucosal leukoplakia, nail abnormalities, hyperkeratosis, and hyperhidrosis of the palms and the sole. In Pachyonychia congenita the nails become thick and shed at an early age and the mucosal leukoplakia do not undergo malignant transformation. Haematological abnormalities do not occur in pachyonychia congenita (16). White spongy nevus is a congenital leukokeratosis that presents with diffuse milky-white plaques on oral mucous membrane. The keratotic plaques are extensive and persist throughout life, without a tendency for malignant transformation. It is not associated with skin, nail or hematological abnormalities as seen in DKC (16).

Diagnosis

Accurate diagnosis of DKC is critical, especially because therapy for complications, such as BMF or cancer, often is urgent (3). Appropriate tests should be performed to screen for bone marrow failure, pulmonary disease, neurological disease and mucosal malignancies. These include complete blood count, chest radiograph, pulmonary function tests, and stool for occult blood. Mutation analysis is useful in conforming diagnosis. Genetic testing for occult DKC should be considered in patients with aplastic anaemia. Patients and family members without a known mutation can be screened with leukocyte subset flow fluorescence in situ hybridization (flow-FISH), which can identify very short telomeres in both clinically apparent and silent disease (18). Patients who have BMF in whom Fanconi anemia is ruled out (normal chromosome breakage test with cross linking agents) should have telomere length tested by flow-FISH in leukocytes to evaluate for DKC. This is the most sensitive and specific screening test for DKC.

Treatment

There is no effective and curative treatment for DKC. Some interceptive and preventive measures can be adopted for which an early diagnosis is essential. Patient should be kept under observation and recalled for periodic follow up (16). Patients with DKC are at high risk for malignancies and bone marrow failure, frequent monitoring for early detection of these complications is recommended. Screening annually by a head and neck specialist and semi-annually by a dentist is warranted. Clinical tests for disease surveillance include at least twice-yearly complete blood counts; annual bone marrow aspirates, biopsies, and cytogenetic; annual pulmonary function tests; gynaecologic examinations; and skin cancer screening by a dermatologist (3). The medical management of DKC is complex and must be based on patient-specific needs. Short term treatment options for bone marrow failure (BMF) in patients with DKC include anabolic steroids (oxymethalone), granulocyte macrophage colony-stimulating factor, granulocyte

colony-stimulating factor, and erythropoietin (19). However, the long-term curative option is hematopoietic stem cell transplantation (HSCT). Following the model of the Fanconi anemia consensus guidelines (3) , treatment of BMF is recommended if the haemoglobin is consistently below 8 g/dL, platelets less than 30,000/mm^3, and neutrophils below 1000/mm^3. Stem cell transplantation from matched sibling donor is currently the treatment of choice. It requires modified nonmyeloablative conditioning protocols, since the patients with DC are prone to pulmonary and hepatic complications (10). In future gene therapy can provide an alternative therapy for management of this fatal condition (16). In families where mutations in the DKC1 and TERC gene have been known antenatal diagnosis is possible (20).

Conclusion

DKC is a multisystem disorder that predisposes to BMF and cancer. Patients should be monitored closely for these and other complications. In recent past, identification of large numbers of patients who have DKC has led to the recognition of a broad clinical phenotype and an appreciation that these patients have abnormalities in telomere biology. Mutations in genes involved in telomere biology have been identified in DKC. Measurement of telomere length in leukocyte subsets determined by flow-FISH is a sensitive and specific screening test for DKC in patients who have BMF and normal chromosome breakage tests. The only long term cure for the haemopoietic abnormalities is allogeneic haematopoietic stem cell transplantation.

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