Cancer Association of South Africa (CANSA)

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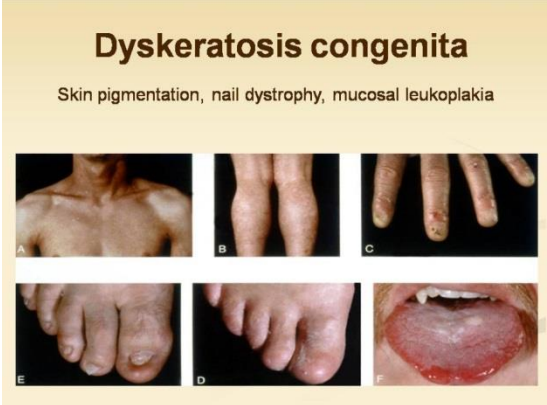
Fact Sheet
on
Dyskeratosis Congenita

Introduction

Dyskeratosis Congenita (DKC), also called Zinsser-Cole-Engman syndrome, is a rare progressive congenital (born with) disorder that in some ways resemble premature aging (similar to progeria). The disease mainly affects the integumentary system (i.e, the skin, the organ system that protects the body from damage), with a major consequence being anomalies of bone marrow.



[Picture Credit: Dyskeratosis Congenita]

Synonyms for Dyskeratosis Congenita include:

- DC
- DKC
- Dysfunctional telomere maintenance
- Dyskeratosis congenita syndrome
- Short telomere disease
- Zinsser Cole Engeman syndrome
- Hoyeraal Hreidarsson syndrome

Dyskeratosis Congenita (DKC)

Dyskeratosis congenita is a disorder that can affect many parts of the body. There are three features that are characteristic of this disorder: fingernails and toenails that grow poorly or are abnormally shaped (nail dystrophy); changes in skin colouring (pigmentation), especially on the neck and chest, in a pattern often described as ‘lacy’; and white patches inside the mouth (oral leukoplakia).

People with dyskeratosis congenita have an increased risk of developing several life-threatening conditions. They are especially vulnerable to disorders that impair bone marrow function. These disorders disrupt the ability of the bone marrow to produce new blood cells. Affected individuals may develop aplastic anaemia, also known as bone marrow failure, which occurs when the bone marrow does not produce enough new blood cells. They are also at higher than average risk for myelodysplastic syndrome, a condition in which

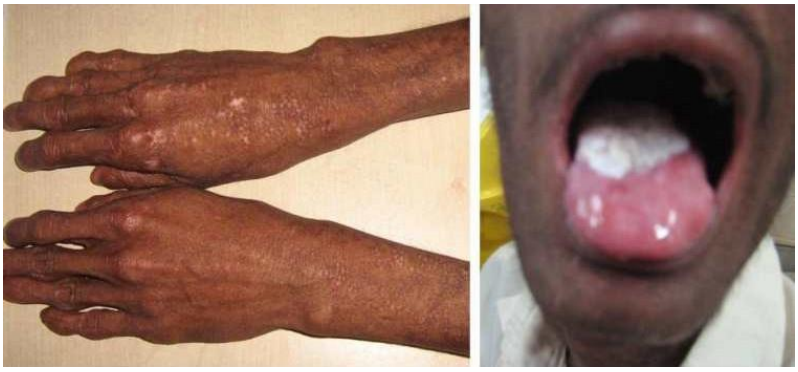
immature blood cells fail to develop normally; this condition may progress to a form of blood cancer called leukaemia. People with dyskeratosis congenita are also at increased risk of developing leukaemia even if they never develop myelodysplastic syndrome. (Please refer to the Fact Sheet on Myelodysplastic Syndrome). In addition, they have a higher than average risk of developing other cancers, especially cancers of the head, neck, anus, or genitals.

People with dyskeratosis congenita may also develop pulmonary fibrosis, a condition that causes scar tissue (fibrosis) to build up in the lungs, decreasing the transport of oxygen into the bloodstream.

Additional signs and symptoms that occur in some people with dyskeratosis congenita include eye abnormalities such as narrow tear ducts that may become blocked, preventing drainage of tears and leading to eyelid irritation; dental problems; hair loss or prematurely grey hair; low bone mineral density (osteoporosis); degeneration (avascular necrosis) of the hip and shoulder joints; or liver disease. Some affected males may have narrowing (stenosis) of the urethra, which is the tube that carries urine out of the body from the bladder. Urethral stenosis may lead to difficult or painful urination and urinary tract infections.

The severity of dyskeratosis congenita varies widely among affected individuals. The least severely affected individuals have only a few mild physical features of the disorder and normal bone marrow function. More severely affected individuals have many of the characteristic physical features and experience bone marrow failure, cancer, or pulmonary fibrosis by early adulthood.

[Picture Credit: Dyskeratosis Congenita 2]



While most people with dyskeratosis congenita have normal intelligence and development of motor skills such as standing and walking, developmental delay may occur in some severely affected individuals. In one severe form of the disorder called Hoyeraal Hreidaarsson syndrome, affected individuals have an unusually small and underdeveloped cerebellum, which is the part of the brain that coordinates movement. Another severe variant called Revesz syndrome involves abnormalities in the light-sensitive tissue at the back of the eye (retina) in addition to the other symptoms of dyskeratosis congenita.
(Genetics Home Refere4nce).

The disease is characterised by multisystem failure, affecting essentially tissues with a high proliferation rate: skin, mucous membranes and bone marrow.

- Short stature (16%)
- Cutaneous signs:
    - Hyperpigmentation, telangiectasia, atrophy (poikilodermia)
    - Dystrophic nails and palmoplantar keratoderma, hyperhidrosis
    - Mucosal leukoplakia
    - Dental caries or loss (18%)
    - Blepharitis, conjunctivitis, epiphora (36%)
    - Sparse eyebrows / eyelashes
    - Alopecia (16%)

        - Urethral stricture, phimosis (7%)
    - Bone marrow failure, peripheral pancytopenia (93%)
    - Other sings:
        - Oesophageal stricture (14%)
        - Pulmonary fibrosis (19%)
        - Liver cirrhosis (5%)
        - Hypogonadism (8%)
        - Abnormal bvone trabeculation, osteoporosis (4%)
    - Immune abnormalities: reduced or increased immunoglobulin level, T- and/or B-lymphocyte deficiency
    - Mild mental retardation, learning difficulties (21%)
    - About 90% of affected individuals are males

(Atlas of Genetics and Cytogenetics in Oncology and Haematology)

Occurrence of Leukaemia and Cancer

Individuals with Dyskeratosis Congenita also have a predisposition to develop leukaemia and cancer (malignancy) especially squamous cell carcinoma of the head and neck, and especially at the site of leukoplakia. If cancer occurs, it usually does not develop until the age of about 30. Thus, leukaemia and cancer are more common in individuals who have a moderate or milder form of Dyskeratosis Congenita. Individuals who underwent a stem cell or bone marrow transplant for the treatment of their bone marrow failure are also at risk of developing cancer later in life. In rare cases leukaemia or cancer may be the first manifestation of disease (NORD).

Dyskeratosis Congenita (DKC) in Children

Dyskeratosis Congenita (DKC) is caused by a change (mutation) in genes. Sometimes, this change happens in a child with DKC without being passed on by their parents. Most often, though, the genes that are not working correctly are passed to children by their parents. Some parents of children with DKC may have the disease but might not have obvious signs of it.

Babies are born with Dyskeratosis Congenita, although symptoms of the disease may not show up for years, and sometimes even for decades. Some babies are diagnosed with Dyskeratosis Congenita soon after they are born. Other people do not get a diagnosis until they are adults. Most often, doctors find the disorder when a person is between 10 and 30 years old.

(Seattle Children's Hospital Research Foundation).

Incidence of Dyskeratosis Congenita (DKC) in South Africa

Because Dyskeratotis Congenita is primarily a non-cancerous condition, the National Cancer Registry (2010) does not provide any information on this condition. DKC is a precursor to blood problems, including leukaemia.

The South African National Cancer Registry (2010) does not provide information regarding the different types of leukaemia – they are all grouped together and listed as 'Leukaemia'.

According to the National Cancer Registry (2010) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2010:

In providing the incidence figures of leukaemia in South Africa, The National Cancer Registry does not make provision for the reporting of the different types of leukaemia – it also does not differentiate between acute and chronic leukaemia - neither does it provide for different statistics for cases of adult and childhood leukaemia.

According to the National Cancer Registry (2010) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2010:

Group - Males 2010	No of Cases	Lifetime Risk	Percentage of All Cancers
All males	349	1:617	1,29%
Asian males	9	1:522	1,29%
Black males	181	1:1 044	1,71%
Coloured males	46	1:311	1,53%
White males	110	1:285	0,87%

Group - Females 2010	No of Cases	Lifetime Risk	Percentage of All Cancers
All females	268	1:991	0,90%
Asian females	3	1:2 989	0,32%
Black females	148	1:1 283	0,95%
Coloured females	41	1:684	1,31%
White females	76	1:416	0,76%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2010 was as follows (National Cancer Registry, 2010):

Group - Males 2010	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	99	28	30	42	48	44	43	11
Asian males	3	1	0	0	0	5	0	0
Black males	61	18	18	22	24	8	14	4
Coloured males	17	2	3	3	6	8	7	0
White males	17	4	7	12	15	22	22	6

Group - Females 2010	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	75	28	25	40	28	31	34	4
Asian females	1	1	0	1	0	0	0	0
Black females	41	16	14	26	14	15	15	0
Coloured females	16	5	3	6	0	5	4	0
White females	17	5	6	7	12	9	14	4

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Causes of Dyskeratosis Congenita (DKC)

To date, there are 10 known genes that identify with DKC - *DCK1*, *TERC*, *TERT*, *NOP10*, *NHP2*, *TINF2*, *USB1*, *TCAB1*, *CTC1*, and *RTEL1*).

DKC is genetically heterogeneous, with X-linked recessive (Mendelian Inheritance in Man [MIM] 305000), autosomal dominant (MIM 127550), and autosomal recessive (MIM 224230)

subtypes. DKC is related to telomerase dysfunction; all genes associated with this syndrome (i.e., *DKC1*, *TERT, TERC, NOP10*) encode proteins in the telomerase complex responsible for maintaining telomeres at the ends of chromosomes regarding shortening length, protection, and replication.

In the X-linked recessive form, the gene defect lies in the *DKC1* gene (located at Xq28), which encodes for the protein dyskerin. Dyskerin is composed of 514 amino acids and has a role in ribosomal RNA processing and telomere maintenance. Modification of dyskerin by SUMOylation has been shown to stabilize the protein. In addition, a mutation in the *DKC1* gene is also found on exon 15, revealing a duplication, which adds a lysine residue on a polylysine tract on the C-terminus. All in all, there have been over 50 mutations found in *DKC1*.

In the autosomal dominant form, mutations in the RNA component of telomerase (*TERC*) or telomerase reverse transcriptase (*TERT*) are responsible for disease phenotype.

Defects in the *NOP10* gene were found in association with autosomal recessive DKC. *NOP10* encodes small nucleolar ribonucleoproteins (snoRNP) associated with the telomerase complex. In persons with autosomal dominant DKC and in terc-/- knockout mice, genetic anticipation (i.e., increasing severity and/or earlier disease presentation with each successive generation) has been reported.

A heterozygous mutation was found on the conserved telomere maintenance component 1 gene (*CTC1*). This implication is also associated with a pleiotropic syndrome, Coats plus.

Homozygous autosomal recessive mutations in *RTEL1* lead to similar phenotypes that parallel with Hoyeraal-Hreidarsson (HH) syndrome. It is associated with short, heterogeneous telomeres. In the presence of functional DNA replication, *RTEL1*mutations produce a large amount of extrachromosomal T-circles. Enzymes remove the T-circles and therefore shorten the telomere. *RTEL1* has a role in managing DNA damage by increasing sensitivity; therefore, mutations on this gene cause both telomeric and nontelomeric causes of DKC.

Patients with DKC have reduced telomerase activity and abnormally short tracts of telomeric DNA compared with normal controls. Telomeres are repeat structures found at the ends of chromosomes that function to stabilize chromosomes. With each round of cell division, the length of telomeres is shortened and the enzyme telomerase compensates by maintaining telomere length in germline and stem cells. Because telomeres function to maintain chromosomal stability, telomerase has a critical role in preventing cellular senescence and cancer progression. Rapidly proliferating tissues with the greatest need for telomere maintenance (e.g, bone marrow) are at greatest risk for failure.*DKC1* has been found to be a direct target of the c-*myc* oncogene, strengthening the connection between DKC and malignancy.

Analysis of 270 families in the DKC registry found that mutations in dyskerin (*DKC1*), *TERT*, and *TERC* only account for 64% of patients, with an additional 1% due to *NOP10*, suggesting that other genes associated with this syndrome are, as yet, unidentified. In addition to the mutations that directly affect telomere length, recent studies also indicate that a DKC diagnosis should not be based solely on the length of the telomere, but also the fact that there are defects in telomere replication and protection. In addition, revertant mosaicism has been a new recurrent event in DKC.
(Medscape).

Prognosis (Outcome)
The major part of patients die before 20 years, mainly from infectious complications of immune deficiency.

- 90% of patients have haematological abnormalities when 30 year-old, and bone marrow failure is the main cause of early morbidity in 71% of cases. It can evolve toward aplastic anaemia or myelodysplasia.
- The mucosal leukoplakia can transform into spinocellular carcinoma.
- Other carcinomas can develop during the third decade of life: lung, colon, larynx, oesophagus, pancreas, Hodgkin's disease.

(Atlas of Genetics and Cytogenetics in Oncology and Haematology)

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