Telomere Biology Disorders (TBD), including Dyskeratosis Congenita (DC), are complex, genetic, multi-system disorders that cause premature. aging of cells and organs. The clinical symptoms of TBDs are varied and require multi-disciplinary diagnosis, monitoring and management

Dermatology 1

Nails: Dystrophic / ridged / split / absent / hypoplastic finger & toenails.
Skin: Lacy reticular / hypo / hyper pigmentation (may be more pronounced on sun exposed areas and flexures), mucosal leukoplakia (early onset), telangiectasia, thin skin, loss of fingerprints, hyperkeratosis (exacerbated by physical factors such as cold, repeated trauma or other irritation), hyperhidrosis / hypohidrosis, increased risk of squamous cell carcinoma at young age
Hair: Alopecia, hair thinning, early greying of hair.
Eyes: Lacrimal stenosis. Abnormal eye lash growth can cause corneal damage. (See Ophthalmology Information Sheet)
Secondary manifestations: Post transplant Graft Versus Host Disease (GVHD) may mimic the features listed above.

Niewisch MR, Beier F, Savage SA. Clinical manifestations of telomere biology disorders in adults. Hematology Am Soc Hematol Educ Program. 2023 Dec 8;2023(1):563-572.doi: 10.1182/hematology.2023000490. PMID: 38066848; PMCID: PMC10726987

Investigate

- Baseline assessment **Family history critical**
- Investigate unusual pigmentation

- Investigate nail dystrophy

- Appropriate referrals to oral medicine / ENT opthalmology

Manage

- Ensure well maintained nails to minimise trauma consider biotin
- Hyperhydrosis symptomatic treatment
- **Refer to specialist in Telomere Biology Disorders contact TeloNet** info@dcaction.org
- Hair loss - consider minoxidil or bimatoprost opthal solution (eyelash/brow loss)
- Treatment as appropriate2, such as emollients/ urea/salicylic acid

Monitor

- Avoid direct sun exposure (around 11am-3pm in UK Mar-Oct)
- Protect skin with clothing, including hat & sunglasses (with UV protection)
- Daily use sunscreen with UVA***** UVB SPF50
- **MDT monitoring and care essential**
- Routine 6 monthly dental appointments oral mucosa monitoring for leukoplakia3
- Annual inspection of skin & mucosae biopsy where appropriate
- Consider clinical photography for monitoring purposes

1 Dyskeratosis congenita. NEJM Images in Clinical Medicine. 2017, N Engl J Med 376;15. DOI:10.1056/NEJMicm1613081
2 No TBD specific treatments currently indicated: danazol/other attenuated androgen, metformin or other telomere-preserving treatments theoretically helpful
3 Local dental practitioners may need to be made aware of the increased risk of Squamous Cell Carcinoma in TBD.

Telomere Biology Disorders (TBD), including Dyskeratosis Congenita (DC) are inherited genetic conditions with variable phenotypes, depending on the genes involved and other epigenetic factors. Telomere length and genetic testing is used as a diagnostic tool. Clinical manifestations include bone marrow failure, liver cirrhosis, pulmonary fibrosis, increased risk of head and neck and genitourinary cancers, stenosis and immunological features. A diagnostic feature can be the "classic triad' of reticulate skin pigmentation, nail dystrophy and oral leukoplakia but these mucocutaneous features can present individually in combination with the above.

Mutations in ACD, TINF2, DKC1, DCLRE1B, NHP2, NOP10, NPM1, POT1, RPA1, PARN, RTEL1, TERT, TERC, MDM4, ZCCHC8, WRAP53 and TYMS-ENOSFI genes, all involved in telomere biology, have been identified in patients with a spectrum of clinical manifestations. Patients with TBDs can respond to danazol (or other attenuated androgens) but allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative option for progressive marrow failure, myelodysplastic syndrome, or leukaemia related to DC and TBDs. Underlying chromosomal instability and sensitivity to chemotherapy and radiation preclude traditional conditioning regimens. Reduced intensity conditioning regimens are recommended. 1,2,3

Sixty patients with a genetic diagnosis of DC were included in a longitudinal cohort study and the presence of 'triad' features were extracted from dermatology records and photographs. The 'classical triad' features and 8 additional mucocutaneous findings (adermatoglyphia, palmoplantar hyperkeratosis, hyperhidrosis, premature greying, scalp or eyelash hair loss, epiphora, and lash irritation / blepharitis) are described. The complete clinical triad manifested in only 37% of patients and 10% lacked all triad features. The study concluded that severe mucocutaneous phenotypes, as defined by the number of triad features and additional findings, are associated with higher-risk genotypes and poorer prognosis compared with milder mucocutaneous phenotypes. Careful detection and monitoring of all mucocutaneous features of DC / TBDs is recommended to enable early referral, confirmatory testing, and appropriate multi-disciplinary clinical management. 2,4

Ratnasamy et al describe the diagnostic and genetic work up and pedigree analysis in a case study of a patient presenting with recurrent febrile episodes and reticulate skin pigmentation interspersed with hypopigmented macules involving the face, neck and extremities, hyperkeratosis of palms and soles, nail dystrophy, leukoplakia of the tongue, premature greying of hair, watery eyes and dental caries. Several of his male relatives were affected with a similar condition. The authors suggest that 'primary care physicians, dentists, and dermatologists should be vigilant enough to diagnose this rare condition in their clinical practice, where patients may present with recurrent febrile illnesses, dental problems, and skin or nail changes for routine evaluation'. 5 Data from literature reviews and groups (cohorts) of individuals with DC / TBDs have identified an overall increased risk of several cancers in affected individuals. 2,6,7

1 Savage SA, Niewisch MR. Dyskeratosis Congenita and Related Telomere Biology Disorders. 2009 Nov 12 [Updated 2023 Jan 19]. In: Adam MP, Mirzaa GM, Pagon, RA, et al eds.GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from https://www.ncbi.nlm.nih.gov/books/NBK22301/

2 Team Telomere Diagnosis and Management Guidelines 2022 https://teamtelomere.org/telomere-biology-disorders-diagnosis-and-management-guidelines-downloads/

3 Tummala H, Walne A, Dokal I. The biology and management of dyskeratosis congenita and related disorders of telomeres. Expert Rev Hematol. 2022 Aug;15(8):685-696. doi: 10.1080/17474086.2022.2108784.

4 Ward SC et al. Beyond the triad: Inheritance, mucocutaneous phenotype, and mortality in a cohort of patients with dyskeratosis congenita. J Am Acad Dematol. 2018 Volume 78, Issue 4, Pages 804– 806 https://www.jaad.org/article/S0190-9622(17)32543-4/pdf

5 Ratnasamy V et al. Dyskeratosis congenita with a novel genetic variant in the DKC1 gene: a case report. BMC Medical Genetics (2018) 19. Article number: 85. https://bmcmedgenet.biomedcentral.com/articles/10.1186/s12881-018-0584-y

6 Alter BP, Giri N, Savage SA, Rosenberg PS. Cancer in the National Cancer Institute inherited bone marrow failure syndrome cohort after fifteen years of follow-up. Haematologica. 2018 Jan;103(1):30-39. doi: 10.3324/haematol.2017.178111.

7 Niewisch MR, Kim J, Giri N, Lunger JC, McReynolds LJ, Savage SA. Genotype and Associated Cancer Risk in Individuals With Telomere Biology Disorders. JAMA Netw Open. 2024 Dec 2;7(12):e2450111. doi: 10.1001/jamanetworkopen.2024.50111.