Telomere Biology Disorders (TBD) including Dyskeratosis Congenita (DC) are complex multi-system disorders that cause premature aging of cells and organs. The clinical symptoms of TBDs are varied but can include IPF, bone marrow failure, liver fibrosis and a pre-dispostion to cancer

HAEMATOLOGY MANIFESTATIONS

Childhood or adult-onset bone marrow hypoplasia or bone marrow failure resulting in cytopaenias, raised MCV, raised HbF, Myelodysplasia, CML, Low urate.

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., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK22301/

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.

Hemanth Tummala, Amanda Walne & Inderjeet Dokal (2022) The biology and management of dyskeratosis congenita and related disorders of telomeres, Expert Review of Hematology, 15:8, 685-696, DOI: 10.1080/17474086.2022.2108784

Investigate

- Bone marrow aspiration and biopsy cytogenetic analysis
- Exclude and treat other/additional causes of high MCV/cytopenia
- Bone marrow fluorescence in situ hybridization (FISH) to detect 5q-, 7q-/monosomy 7, or trisomy 8 and 20q- if clinically indicated
- Blood count G-banding with MCV, differential and reticulocyte count at least annually
- Telomere length FlowFish / STELA**
- Genomes England panel Cytopenia - NOT Fanconi Anaemia (R91)
- **Family History**
  premature greying
  nail dysplasia
  leukoplakia
  abnormal skin pigmentation

Manage

- Limited data re: colony stimulating factors e.g. GCSF, erythropoietin Eltrombopag 2
- Minimise ionising radiation exposure
  Avoid DNA damaging agents & prednisolone
- Early consideration of bone marrow/ stem cell transplant + donors
- **Refer to specialist in Telomere Biology Disorders contact TeloNet**
  info@dcaction.org
- Consider attenuated androgens / non attenuated androgens / Oestrogen 1,2,3,4 * +
- Immuno suppression is usually ineffective and may be harmful in TBDs
- Transfusion - early treatment to prevent iron overload required in view of pre-existing risk of liver involvement
- HSCT - Use nonmyeloablative / minimally myeloablative conditioning protocol 1,2,4,5

Monitor

- **MDT monitoring and care essential**
- Risk of pulmonary disease following HSCT for Telomere Biology Disorders

* Non-attenuated androgens / oxymetholone. Low dose danazol (200mg daily).
Oestrogens in females not deleterious and may be beneficial

\+ There are no currently licensed treatments for TBDs

** Single Telomere Length Analysis https://www.telonostix.com/ TeloNostiX Ltd. Central Biotechnology Services, Henry Wellcome Building, Heath Park, Cardiff, CF14 4XN, UK.

Telomere Biology Disorders (TBD) affect progenitor stem cell production and cell replication in multiple organ systems. Dyskeratosis Congenita (DC) is a severe TBD presenting in early childhood with a clinical triad of nail dysplasia, oral leukoplakia, and abnormal skin pigmentation, associated with bone marrow failure. Alterations 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. These include pulmonary fibrosis, emphysema, cryptogenic liver cirrhosis, lacrimal duct, oesophageal and urethral stenosis, avascular necrosis of hips and shoulders, periodontal disease, an increased predisposition to epithelial and hematologic malignancies plus premature greying of hair. Classical DC is characterized by extremely short telomeres but different gene mutations in an array of telomere maintenance genes can produce variable phenotypes, differing in severity, in childhood or later into adulthood. The symptoms of TBD can appear at any age and adult-onset bone marrow failure can be difficult to distinguish from idiopathic aplastic anaemia. 1,2,3,4

For a suggested diagnostic algorithm for germline telomere diseases see: Townsley DM et al. Bone marrow failure and the telomeropathies. Blood. 2014;124(18):2775–2783. doi:10.1182/blood-2014-05-526285 and Tummala et al Ref 1.

Medical Management of Bone Marrow Failure

Significant peripheral cytopenia should be managed with supportive therapy (blood and platelet transfusions). Khincha et al describe the use of the anabolic steroid oxymetholone to treat bone marrow failure.5 Also Danazol was found to be effective in preserving and elongating telomeres in association with a haematological response in patients with telomere diseases.6,7 A personal observation by Prof Inderjeet Dokal suggests patients with TBDs can respond to a dose as low as 0.25 mg oxymetholone/kg per day which can be increased, if necessary, to 2-5 mg/kg per day.1,2 However a 2018 retrospective observational study found that telomere length for age shortened over time in patients with Dyskeratosis Congenita, irrespective of treatment with androgens and recommend that prospective long-term research is needed. 8 **NB:** No androgen therapy is licensed for treatment of TBD.

Stem Cell Transplantation and conditioning regimens

At the present time, 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. 1,2,9,10

TBDs are multisystem disorders requiring expert multidisciplinary monitoring, care and management. Monitoring should include cardiology, respiratory, gastroenterology, hepatology, immunology, ophthalmology, orthopaedics and cancer screening. See Ref 2 chapter 27.

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