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Dyskeratosis Congenita: The First NIH Clinical Research Workshop

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Abstract

Dyskeratosis congenita (DC) is a heterogeneous inherited bone marrow failure syndrome, characterized by abnormally short telomeres and mutations in telomere biology genes. The spectrum of telomere biology disorders is growing and the clinical management of these patients is complex. A DC-specific workshop was held at the NIH on September 19, 2008; participants included physicians, patients with DC, their family members, and representatives from other support groups. Data from the UK's DC Registry and the NCI's DC cohort were described. Updates on the function of the known DC genes were presented. Clinical aspects discussed

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included androgen therapy, stem cell transplant, cancer risk, and cancer screening. Families with DC met for the first time and formed a family support group (http://www.dcoutreach.com/). Ongoing, open collaboration between the clinical, scientific, and family communities is required for continued improvement in our understanding of DC and the clinical consequences of telomeric defects.

Keywords

dyskeratosis congenita; bone marrow failure; telomere

Dyskeratosis congenita (DC) is an inherited bone marrow failure syndrome (IBMFS) characterized clinically by the triad of abnormal nails, reticular skin pigmentation, and oral leukoplakia. Patients with DC are also at very high risk of developing leukemia, solid tumors, and pulmonary fibrosis [1,2]. They have very short germline telomeres, and at least one-half have mutations in known telomere biology genes.

The first clinical research workshop on DC was held on September 19, 2008 at the National Institutes of Health (NIH) in Bethesda, MD. The primary goals for the workshop were to discuss clinical and molecular advances in understanding the pathology of DC, identify areas for future collaboration, bring patients with DC and their families together, and assist them with the organization of a DC family support group. The 80 workshop participants included 42 family members representing 17 families, as well as clinicians, scientists, and representatives from other family support groups.

Studies of Dyskeratosis Congenita

The first case report that linked skin pigmentation, oral leukoplakia, and nail dystrophy was in 1910 [3]. Subsequently, bone marrow and other abnormalities were identified in similar patients. The locus for the X-linked recessive (XLR) form of DC was mapped in the mid-1980s, and the dyskerin gene (*DKC1*) was cloned in 1998 [4,5,6]. Since then there has been rapid progress in understanding the pathogenesis of DC. This was associated with the observation that patients with DC had abnormally short telomeres, and that *DKC1* is involved in telomere length regulation.

The Dyskeratosis Congenita Registry was founded in 1995 at the Hammersmith Hospital in London, UK [7]. It relocated to the Royal London Hospital in 2006 and is administered by Dr. Dokal. This invaluable resource has created the largest database of patients and their families, comprised of 470 patients from 313 families.

The National Cancer Institute (NCI) is conducting a prospective cohort study of DC within its larger IBMFS study (http://marrowfailure.cancer.gov). It opened to accrual in January 2002, and is a comprehensive study designed to prospectively evaluate patients with any IBMFS and their family members (affected and unaffected). Detailed medical history and epidemiology questionnaires are completed by study participants, who all enter the Field Cohort. The IBMFS study team reviews the questionnaires and medical records, consults with home physicians, and determines study eligibility. The Clinic Cohort consists of patients and their family members who also receive comprehensive evaluations at the NIH Clinical Center. Participants are monitored prospectively to determine disease-specific complications and the rate at which they develop. Genetic counseling is provided before and after mutation testing. Between January 2002 and August 2008, the DC cohort had enrolled 43 families: 28 in the Clinic and 15 just in the Field Cohort.

Genetics and Genetic Testing

Approximately 50% of patients with DC have a mutation in one of six genes important in telomere biology. DC pedigrees indicate XLR, autosomal dominant (AD), and autosomal recessive (AR) inheritance. Dyskerin (*DKC1*), the X-linked DC-associated gene, regulates telomerase, the enzyme that adds nucleotide repeats to telomere ends [4]. Primary fibroblasts and lymphoblasts of males with *DKC1* mutations were shown to have very short telomeres [8,9]. There are more than thirty different amino-acid mutations of the dyskerin protein. Recent studies suggest that telomerase replacement can restore the telomere maintenance deficiency in subtypes of X-linked DC cells [10]. Research directions discussed at the workshop included testing the efficacy of dyskerin gene replacement techniques to restore normal activity in X-linked DC cells.

Three genes have been identified in AD DC, including the RNA subunit of telomerase (*TERC*), the telomerase enzyme (*TERT*), and a component of the shelterin telomere protection complex (*TINF2*) [11,12,13,14,15,16,17,18]. In a small number of families, DC is inherited in an AR manner. AR inheritance of mutations in NOP10 or NHP2 (gene names *NOLA3* and *NOLA2*, respectively), components of H/ACA snoRNP complexes which regulate telomerase, were identified in three consanguineous families with DC [19,20]. Homozygous *TERT* and *TERC* mutations have also been described [21,22].

TERT and *TERC* mutations have been found in patients with pulmonary fibrosis and patients with apparently acquired aplastic anemia; these patients did not have the classic triad of DC [23,18,24,25]. This suggests that both pulmonary fibrosis and aplastic anemia are part of a broader clinical spectrum of patients with disorders of telomere biology.

Genetic testing in patients with suspected DC should be considered after careful assessment of the family history. Genetic counseling before and after mutation testing is critical; testing may identify unsuspected affected or carrier diagnoses of DC, influencing both health care and family dynamics. Complex issues need to be considered regarding counseling and testing of children and adolescents. Pre-pregnancy and/or prenatal genetic counseling is available for families considering the risk to future offspring.

Clinical Findings in Dyskeratosis Congenita

The diagnosis of DC can be challenging because of its clinical heterogeneity. Telomere length determination by multicolor flow cytometry and fluorescence *in situ* hybridization (flow-FISH) in lymphocytes and lymphocyte subsets was shown to be sensitive and specific for the distinction of patients with DC from unaffected family members; it also identifies silent mutation carriers [26]. Analyses of follow-up data were discussed at the workshop which suggests that this test clearly distinguishes patients with DC from patients with other IBMFS or acquired aplastic anemia. However, telomeres may be very short in apparently unaffected relatives of patients with DC. There was some controversy regarding the management of these individuals. They may be silent carriers of an unidentified gene mutation. Ongoing follow-up of these family members will be important in understanding the clinical consequences of short telomeres. Novel clinical findings in the NCI DC cohort were presented and the clinical recommendations discussed are presented in Table 1.

Management of DC

The clinical management of DC is complex and randomized clinical trials are lacking. Following the model of the Fanconi Anemia consensus guidelines, treatment of bone marrow failure is recommended if the hemoglobin is consistently below 8 g/dL, platelets less than 30,000/mm^3, and neutrophils below 1000/mm^3 [27]. The first consideration for

treatment for any hematologic problem should be HCT, if there is a matched related donor, proven to not have DC by physical and laboratory examinations, mutation testing and/or telomere length assay. HCT from an unrelated donor can be considered, although a trial of androgen therapy may be chosen.

Based on experience in the NCI Cohort, patients with DC appear to be sensitive to androgens, and the dose must be adjusted to avoid such side effects as impaired liver function or behavioral problems (i.e. aggression, mood swings). Splenic peliosis occurred in two patients with DC receiving the combination of androgens and G-CSF, leading to the recommendation that this combination be avoided [28]. G-CSF with erythropoietin has occasionally been useful but should not be used in combination with androgens. Failure of DC-related BMF to respond to the type of immunosuppression used in acquired aplastic anemia suggest that the original diagnosis was not correct [29].

HCT is the only definitive treatment for marrow failure. A reduced intensity conditioning regimen tailored for patients with DC was described. Its goal is to minimize the peri-transplant and late toxicity associated with transplant. Two of the four evaluable patients in the study survived. One died due to an adenoviral infection. Another had graft failure, was re-transplanted, and had early evidence of engraftment, but chose to leave the hospital early following the second stem cell infusion and died of sepsis. Of the 2 patients that remain alive, both are engrafted. One was the recipient of a matched related peripheral blood graft, the other a recipient of an unrelated donor marrow infusion. HCT for DC is clearly a life-saving measure but has substantial risks either from toxicity due to radiochemotherapy or immune related complications including rejection and graft versus host disease. Workshop attendees strongly agreed on the need for ongoing studies focused on improving HCT outcomes in DC.

Comprehensive evaluations at diagnosis are suggested, and then ongoing monitoring should be tailored to each patient. Other clinical tests to *consider* for disease surveillance for DC include bi-annual complete blood counts; a baseline and then annual bone marrow aspirates, biopsies, and cytogenetics, liver ultrasounds especially for, but not limited to, those on androgens, and annual pulmonary function tests, gynecologic exams, and skin cancer screening by a dermatologist (Table 1).

Patient and Family Psychosocial Needs

A DC family support group was one of the greatest needs identified by families in the NCI DC cohort. This workshop was used as a forum to bring families with DC together for the first time. Families with DC and representatives from several other family support and advocacy groups attended an afternoon workshop designed to empower the families to form their own support group. The missions, functions, and structure of similar organizations, including the Diamond Blackfan Anemia Foundation, Angioma Alliance, Fanconi Anemia Research Fund, NCI's Consumer Advocates in Research and Related Activities, and SpeciaLove, Inc. were described by their representatives. Interactive discussions with these groups and the families with DC led to the development of a mission statement, action plan, and board of directors. Additional information for the DC family support group can be found at http://www.dcoutreach.com/

Future Directions

The last 10 years have seen great advancement in the understanding of telomere biology and the molecular pathogenesis of DC, but more challenges still need to be addressed. Mutations in six genes are associated with DC, but a mutation in one of these genes is detectable in only about half of clinically-diagnosed patients. Studies of the molecular and cellular

biology of DC will lead to improved understanding of the disease, and may result in the development of novel therapeutic approaches.

Larger studies of telomere length as a diagnostic test utilizing consistent methodology and large numbers of healthy control subjects are needed. Prospective studies are required to better understand the clinical consequences of DC, identify the basis for BMF response to androgens, define the best HCT regimen, and identify the best measures for surveillance of cancer and other complications. These endeavors will be successful if the clinical and scientific communities studying DC, IBMFS, and telomeres work in close and open collaboration both among themselves and with affected families and their support group.

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Table I

Clinical complications of dyskeratosis congenita and suggested monitoring. This is a general list and highlights topics discussed at the Workshop. Management of each patient with DC should be individualized.

System	Finding(s)	Clinical Complications	Suggested Monitoring/Therapy
Dermatologic	Nail dystrophy, skin pigmentation, thinning/early graying of hair, hyperkeratosis of palms/soles, adermatoglyphia, acrocyanosis	Increased skin cancer risk [30]	Annual exams by dermatologist Limit sun exposure Use sunscreen
Oral	Leukoplakia, erythematous patches, brown/black patches, short tooth roots, enlarged dental pulp chambers (taurodontism) [31]	Oral cancer	Annual cancer screening, bi- annual dental exams
Head and Neck		Squamous cell cancer [30]	Annual exams by an otolaryngologist, self-examination, early treatment
Gastrointestinal	Esophageal stenosis; liver fibrosis	Difficulty swallowing; sensitivity to androgens	Esophageal dilatation; monitor liver functions
Ophthalmologic	Excessive tearing (epiphora) due to lacrimal duct obstruction, ectropion, entropion, trichiasis, sparse eyelashes, optic nerve atrophy, retinal vessel fragility and hemorrhages, exudative retinopathy [32,12]	Corneal abrasion, infection, blindness (due to retinal abnormalities)	Symptomatic and annual exams
Neurologic	Cerebellar hypoplasia [33] Microcephaly	Variable, ataxia, learning difficulties	Supportive
Pulmonary	Pulmonary fibrosis	Variable, sometimes seen after bone marrow transplantation	Supportive, annual pulmonary function tests
Orthopedic	Osteoporosis, avascular necrosis of hips and shoulders	Fractures	Calcium and vitamin D supplementation, supportive care
Hematologic	Low blood counts, macrocytic red blood cells	Bone marrow failure; myelodysplastic syndrome	Consider bi-annual complete blood counts (more frequent if clinically indicated) Baseline bone marrow biopsy/aspiration at diagnosis, then consider annual bone marrow biopsy/aspiration and cytogenetics. Treatment should based on degree of bone marrow failure (see text)
		Leukemia	Disease-specific therapy with careful monitoring for treatment-related complications
Gynecologic	Pain or masses	Increased risk of anogenital cancer [30]	Annual gynecologic examinations and as needed