Roni Dodiuk-Gad, Gen Med (Los Angel) 2021, Volume 09

Darier disease – new insights

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Importance: Knowledge about the clinical and genetic features of Darier disease (DD), an orphan autosomal-dominant genetic disorder is sparse and has been evaluated only in few studies.

Objectives: To investigate the clinical and genetic features, health-related quality of life, cognitive functioning, prevalence of Attention Deficit Hyperactivity Disorder (ADHD), bacteriological aspects and ocular manifestations and of a large group of patients with DD.

Design: In this large case series, 76 individuals with Darier Disease (from 3447 families), were evaluated utilizing a structured questionnaire-based interview, a physical examination with focus on cutaneous and ocular assessment, retrospective assessment of their medical records. Quality of life was assessed using 3 questionnaires: DLQI, EQ-5D and one specially designed for the study and cognitive function by neuropsychological evaluation. Bacteria samples were taken from patients' lesional skin, both nares and perineum. Two different methods were used to assess ADHD among the patients: Adult ADHD Self-Report Scale (ASRS).

Setting: An academic-based, dermatology department at Emek Medical Center, Israel.

Participants: Adults aged 18 years or older with a biopsy proven diagnosis of DD.

Results: The most frequent locations of lesions were the hands and fingernails. We found that wart-like lesions on the hands were more visible after soaking the hands in water. We named this phenomenon the "wet hand sign". Oral involvement was found in 43% of patients. Genital involvement was found in 48% of women and 16% of men. Most patients (88%) exhibited a combination of disease patterns (flexural, seborrheic, nevoid and acral). Systemic involvement included neuropsychiatric diseases, recurrent parotid gland obstruction, thyroid disease and ophthalmic disorders. Enormous variability in systemic morbidities was found within patients of each family and among the different families. Twenty-three mutations in ATP2A2 were scattered over the entire gene, 14 of them novel. Darier's disease has a major negative impact on the health-related quality of life (HRQL) of patients and higher scores of both skin area affected and clinical severity are associated with a worse HRQL. Patients with darier's disease have high prevalence of S. aureus colonization in lesional skin and nares, with a correlation between disease severity and extent of colonization.

Patients with darier's disease have high prevalence of learning disabilities, mostly reading difficulties. Sixteen out of the 49 patients assessed (33%) were diagnosed with ADHD. Ocular examination revealed darier disease lesions on the eyelids in 55% of the patients, blepharitis in 44%, conjunctival hyperemia in 28% and short tear film break-up time in 83%.

Conclusions and Relevance: Darier disease is a systemic disease with dominant skin manifestation and important extra-cutaneous symptoms, especially psychiatric, cognitive and ocular. Patients with DD have high prevalence of S. aureus colonization in lesional skin and nares, with a correlation between disease severity and extent of the colonization. Documentation of disease on the hands and fingernails provides a highly sensitive means to aid in the diagnosis of darier disease. It is important to evaluate mucosal lesions including genital and oral mucosa.

The study of darier disease may shed new light on the genetic foundations and pathogenesis of illnesses that are challenging to study, such as neuropsychiatric disorders and learning disabilities.