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Cutaneous features of myotonic dystrophy types 1 and 2: Implication of premature aging and vitamin D homeostasis

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Abstract

Skin changes have been described in myotonic dystrophy type 1 (DM1). However, whether and in which way skin is a target of specific disease alterations in DM1 and DM2 has not been yet clarified. This study aims to explore cutaneous features of DM1 and DM2 patients. Skin examination was performed in 60 DM1, 15 DM2, and 103 control, unselected patients by means of dermoscopy. It revealed quantitative and qualitative abnormalities of nevi and typical signs of premature aging in both DM1 and DM2 patients, with a significantly higher frequency of dysplastic nevi, alopecia, xerosis and seborrheic dermatitis. Twenty-eight nevi were excised in DM patients and none showed histological features of melanoma, although 12 of them were diagnosed as dysplastic and the remaining 16 presented histological irregularity in melanin distribution. In DM1 patients, the number of nevi correlated with CTG expansion size, whereas the presence of dysplastic nevi and xerosis inversely correlated with vitamin D levels. DM1 and DM2 patients display a high frequency of skin abnormalities, the most common of which correlate with genotype severity and serum vitamin D levels. Skin examination is highly informative in these patients and reveals features suggestive of premature aging and impaired vitamin D homeostasis.

Keywords: Myotonic dystrophy type 1; Myotonic dystrophy type 2; Skin abnormalities; Premature aging; Vitamin D

1. Introduction

Myotonic dystrophy (DM) is the most prevalent form of muscular dystrophy among adult Caucasians [1]. DM is an autosomal dominant disease, characterized by myotonia, muscle weakness, cataracts, hypogonadism, frontal balding, cardiac conduction defects and endocrine and central nervous systems involvement. The classic form of the disorder (DM1) is caused by an expanded [CTG]n repeat of the DMPK gene on chromosome 19q13.2 [2]. In a minority of patients, who have mainly proximal weakness, as opposed to the typical distal weakness of DM1, the disease is caused by a [CCTG]n of the *CNBP* gene, in chromosome 3q (DM2) [3]. Although these two forms of the disease present a different pattern of distribution of muscular atrophy at both clinical and histopathological levels, they share a common pathogenesis and a multi-systemic involvement of organs and tissues [4–7]. Skin changes, such as baldness and epithelial tumors (pilomatrixomas and non-melanoma skin cancers (NMSC)), are reportedly common in DM1 patients [8,9]. Vitamin D_3 (cholecalciferol) is a steroid hormone produced in the skin, through the ultraviolet conversion of 7-dehydrocholesterol. It must be metabolized to 25-hydroxyvitamin D (25(OH)D) in the liver and then to 1,25 hydroxyvitamin D ($1,25(OH)_2D$) in the kidney to become active. Vitamin D, besides having a critical role in calcium homeostasis and muscle metabolism, exerts its action on many organs and tissues, including skin itself. Indeed, skin is not only

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the site of vitamin D synthesis, but also one of its target tissues, in terms of epithelial cell proliferation and differentiation [10].

A severe vitamin D deficiency in DM1 and DM2 has been shown in two recent studies [11,12]. The exact mechanisms underlying vitamin D deficiency in DM are not clear, although preliminary evidence sustains the hypothesis that cutaneous alterations, rather than malabsorption or a liver dysfunction, might be responsible for vitamin D deficiency [11].

Since vitamin D and calcium inhibit keratinocyte proliferation, the higher frequency of pilomatrixoma, reported in DM1, might be related to vitamin D deficiency [13]. On the other hand, recent epidemiological studies provided evidence of increased risk of malignant neoplasm, including thyroid, skin, breast, endometrium, brain, ovary and colon cancer, in different DM populations [14,15]. The higher prevalence of benign and malignant tumors in DM1 is reportedly associated with female gender but not with CTG expansion size and lifestyle factors [16,17], although the occurrence of multiple basal, squamous cell carcinomas and dysplastic nevi reported in a DM1 patient suggests that the accumulation of abnormal nuclear RNA might contribute to the malignant skin transformation in myotonic dystrophy [18]. Most recently, two studies showed discordant data on the increased prevalence of pre-neoplastic and neoplastic cutaneous lesions in DM1 [19,20], whereas dermatological studies on DM2 patients have not been performed, to our knowledge.

The aim of the present study was to better define the nature and extension of skin lesions and disorders in both DM1 and DM2 patients, and analyze their relationship with severity of genotype and circulating levels of vitamin D.

2. Patients and methods

We conducted a case–control study on 60 DM1 patients: 34 men and 26 women, mean age 44.6 years (age range 22–67 years), and 15 DM2 patients: 8 men and 7 women, mean age 51.4 years (age range 29–62 years). Enrollment was performed among DM1 and DM2 patients consecutively seen at follow-up during one year at our dedicated outpatient clinic. All patients agreed to enter the study and, therefore, were enrolled without any selection other than diagnosis of DM1/DM2. The patients signed an informed consent form at the time of enrollment. The study protocol was approved by the Ethics Committee of Tor Vergata University Hospital. The control group consists of 103 consecutive subjects referred to our dermatologic outpatient clinic: 42 men and 61 women, mean age 48.1 years (age-range 22–80 years). Clinical and laboratory data of DM1 and DM2 patients are summarized and stratified for genotype subclasses [21] in Table 1.

Diagnosis of DM1 and DM2 was confirmed in all patients by DNA analysis performed at the Genetics Section of Tor Vergata Hospital in the three years prior to dermatological work-up using reported protocols [22]. Briefly, (CTG)n/(CCTG)n repeat expansions were determined using a combination of long-range PCR (LR-PCR) and hybridization with (CTG)5/(CCTG)5 radioactively-labeled probes. Expanded fragments were sized only in DM1 samples where LR-PCR allows to detect the majority of *DMPK* expanded alleles. DM2 mutation sizes have not been determined since the LR-PCR test could amplify only smaller *CNBP* alleles in the range of the expansions.

A clinical dermatological assessment was performed on each patient by three different dermatologists to establish the presence of pigmented lesions (junctional, dysplastic, compound and congenital nevi), NMSC (basal cell carcinoma, squamous cell carcinoma, trichoepithelioma, keratoacanthoma), mesenchymal tumors (dermatofibroma), non-melanocytic benign tumors (seborrheic keratosis, angiomas, pilomatrixoma, lipoma), inflammatory dermatoses (xerosis, seborrheic dermatitis, keratosis pilaris, psoriasis, lichen), and other skin alterations (androgenic alopecia, folliculitis, milia, xanthelasma, skin tags,

Table 1
Clinical and laboratory data of DM1 and DM2 patients.

	DM1 (n = 60)	E1 (%)	E2a (%)	E2b (%)	E2c (%)	E3 (%)	DM2 (n = 15)
Sex (M/F)	34/26	6/9	10/3	11/7	4/3	3/4	8/7
Mean age (yrs)	44.6 ± 12.7	50.6 ± 14	43.4 ± 14.8	38 ± 8.3	47.1 ± 7.3	48.6 ± 8.7	51.4 ± 13.5
Age of onset (yrs)	28 ± 13.1	39 ± 12.7	26.1 ± 12.3	19.2 ± 8.3	27.6 ± 13.3	29.3 ± 10.1	33.1 ± 12.0
CTG repeat number	545 ± 375	109 ± 49	389 ± 75	658 ± 97	891 ± 86	1270 ± 242	\\
MIRS score 1	7	7 (46.6)	0 (0)	0 (0)	0 (0)	0 (0)	\\
2	10	3 (20)	3 (23)	3 (16.6)	1 (14.3)	0 (0)	\\
3	22	4 (26.6)	6 (46)	8 (44.4)	2 (28.6)	2 (28.6)	\\
4	21	1 (6.6)	4 (30.8)	7 (38.9)	4 (57.1)	5 (71.4)	\\
Vitamin D (ng/ml)	15.6 ± 7.2	17.7 ± 7.0	17.1 ± 7.3	12.9 ± 7.5	13.3 ± 4.9	13.7 ± 9	20.3 ± 7.7
Neoplasm	19 (26.6)	3 (20)	4 (30.7)	5 (27.7)	2 (28.6)	5 (71.4)	0
Benign neoplasms		1 Uterine fibroid	1 Uterine fibroid	2 Uterine fibroids; 1 Gallbladder adenoma; 2 Parathyroid adenoma	2 Uterine fibroids	3 Uterine fibroids	
Malignant neoplasms		1 Breast cancer; 1 Thyroid cancer	1 Uterine cancer 1 Kidney cancer 1 Thyroid cancer			1 Lymphoma; 1 Melanoma	

Abbreviations: DM1 (myotonic dystrophy type 1), DM2 (myotonic dystrophy type 2), MIRS (Muscle Impairment Rating Scale).
E1, E2a, E2b, E2c, E3 represent genotype subclasses of DM1 patients according to CTG number: E1 (50–200). E2a (200–500). E2b (500–800). E2c (800–1000). E3 (1000–3000).