

Association of Mal de Meleda with Neurofibromatosis Type 1, in 15-year Old Caucasian Female with Familial History of Neurofibromatosis Type 1. Case Report and Review of the Literature

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Abstract

Observations: Mal de Meleda (MDM) is very rare autosomal recessive genodermatosis disorder characterized by erythema and hyperkeratosis of the palms and soles with sharp demarcation, extending to the dorsal aspects of the hands and feet (known as transgrediens). MDM characterized by genetic and clinical heterogeneity. Neurofibromatosis (NF) is a term that has been applied to a variety of related syndromes, characterized by neuroectodermal tumors arising within multiple organs and autosomal-dominant inheritance. Neurofibromatosis type I (NF-1) is the most common type of the disease accounting 90% of the cases, and is characterized by multiple cafe-au-lait spots and the occurrence of neurofibromas along peripheral nerves.

15-year old Caucasian female was referred to our department with complaint of diffuse severe transgrediens plantar keratoderma accompanied by painful fissures. After appropriate examination diagnosis of MDM and neurofibromatosis type 1 made and therapy with systemic 13-cis-retinoic acid was started, with significant positive effect. To the best of our knowledge this is a first description of coexistence of MDM and neurofibromatosis type 1. 13-cis-retinoic acid demonstrated high clinical efficacy in treatment of MDM in our observation.

Introduction

Mal de Meleda (MDM), also known as keratosis palmoplantaris transgrediens of Siemens, is a very rare genodermatosis with the prevalence in the general population of 1 in 100,000 [1]. The disease was first observed and described in 1826 by Dubrovnik's state-physician Luca Stulli on the Dalmatian island of Mljet (Meleda) in Croatia [2]. Doctor Stulli was the first to describe "Mljet disease", Mal de Meleda, in a paper entitled "Di una varieta

cutanea" in 1826, in a letter to the director of the Florentine journal *Antologia*. This article describes the disease in detail, and emphasizes that it is not an infection, but a hereditary disease, and became a classic of dermatologic literature [3, 4, 5].

Recently, a number of sporadic cases have also been reported in more widespread areas, such as the Middle East, Northern Africa, Turkey, Sweden and Taiwan [6]. Kinship marriages which is not uncommon in the

Caucasus play an important role in the development of MDM as in the development of other genetic diseases.

Neurofibromatosis (NF) is a term that has been applied to a variety of related syndromes, characterized by neuroectodermal tumors arising within multiple organs and autosomal-dominant inheritance. Neurofibromatosis type I (NF-1) is the most common type of the disease accounting 90% of the cases, and is characterized by multiple cafe-au-lait spots and the occurrence of neurofibromas along peripheral nerves [7].

A café-au-lait macule (CALM) is an evenly hyperpigmented, sharply demarcated macule or patch of any size. Generally, CALMs are tan to dark brown and can be of any size and located anywhere on the body except the palms, soles, and scalp and were a common sign of neurofibromatosis type 1 (NF1) and

so-called neurofibromatosis type 1-like syndrome (NLFS) [8].

Here we present a case of MDM in association with familial neurofibromatosis type 1 (NF1).

Case Report

A 15-year old Caucasian female was referred to our department with complaint of diffuse severe transgrediens plantar keratoderma accompanied by painful fissures, which caused gait instability. Several CALMs were noted from birth but later were found to have increased in number and size.

Physical examination revealed the transgrediens sharply demarcated erythema and hyperkeratosis on the dorsal sites of feet, with a predominant involvement of the soles, accompanied with cobblestone-like distribution due to deep fissures (Figure 1). Her fingernails were normal and toenails were slightly thickened. Her palms, hairs and oral mucosa were intact. There is also 7 CALMs (1,7-2,5 cm) on her trunk but no neurofibroma were found.



Figure 1. Diffuse severe transgrediens plantar keratoderma accompanied by painful fissures



Figure 2. Significant improvement of status localis after 2 week of therapy

Vital sign were normal PR 70 per min. BP 110/60 mmHg. BT 36,6° C. Neurologic examination viewed cognitive impairment and low IQ. Here weight was 47 kg, height – 134 cm.

Multiple Lisch nodules (iris hamartomas) were seen on ophthalmologic examination. Cranial CT scan, chest X-ray, abdominal USM, ECG and routine laboratory tests revealed. no pathology. Skin scraping and KOH examination was negative for fungi. Culture for bacteria and fungi from sole lesions and toenails were negative.

Her family consist of father, mother two sisters and two brothers. She was the fourth daughter of unrelated parents. The mother and four siblings were healthy, but detailed family history of skin diseases show that elder brother of mothers had similar fissures on soles.

Physical examination of patients family members revealed clinical signs of NF1 in father: 11 CALMs (2-4 cm), 1 neurofibroma and multiple Lisch nodules were seen on skin and iris respectively. Routine laboratory tests revealed no pathology. Cranial CT scan, chest X-ray, abdominal USM and routine laboratory tests were all normal.

Skin biopsy was not taken due to parents refusal. All of other members of family were healthy.

Diagnosis of MDM associatiated with familial NF1 were made and treatment with isotretinoin 0,5 mg/kg/day, topical salicylic acid 10 %, emollient with methyluracil and chloramphenicol on fissures on plantar region was started with significant improvement after 2 week of therapy (**Figure 2**). Over the next 4 months she remained well and during the next reexamination 4 month later after discontinuation of treatment there was no severe hyperkeratosis as at the time of first visit observed.

Discussion

MDM is genodermatosis with autosomal-recessive inheritance, which clinically characterized by erythema and hyperkeratosis of the palms and soles with sharp demarcation, extending to the dorsal aspects of the hands and feet (transgrediens course). The autosomal-recessive mode of inheritance was described in 1938, and the linkage of the disorder to the 8qter locus was reported in 1998 [9, 10]. Recently, homozygous mutations in the ARS (component B) gene were identified in families with MDM, implicating ARS as the susceptibility gene for this disease [11]. Subsequently, a

patient with MDM lacking mutations in ARS was reported, suggesting genetic heterogeneity [12]. Moreover, MDM is characterized also polymorphism of clinical manifestations, i.e. a clinical and genetic heterogeneity.

A café-au-lait macule (CALM) is an evenly hyperpigmented, sharply demarcated macule or patch of any size. Generally, CALMs are tan to dark brown and can be of any size and located anywhere on the body except the palms, soles, and scalp [8]. CALM are stated to be present soon after birth and to increase in number during the first and second decades of life [13].

CALM, are often noticed in the clinical examination of children of school age [13, 14]. A solitary CALM is a common finding occurring in up to one fourth of all Caucasian school-aged children [15]. 1 or 2 cafe-au-lait spots in a child is a common and normal phenomenon [16]. The finding of three or more CALMs in children with no known underlying disorder is much less frequent at up to 0.3 percent. A study of 41 children with 6 or more CALMs demonstrated that 80 percent were eventually diagnosed with neurofibromatosis type 1 (NF1) [17]. Multiple CALMs may be the only symptom of the disease or a symptom of various diseases and syndromes in combination with other cutaneous and extracutaneous signs. NF type 6 is a rare skin disease with only multiple CALMs.

Neurofibromatosis 1, formerly termed von Recklinghausen's disease, is an autosomal dominant neurocutaneous disorder with a birth incidence of one in 2500 and a minimum prevalence of one in 4–5000 [18]. The Nf1 gene is located on chromosome 17q11.2 and the protein product termed neurofibromin acts as a tumour suppressor [19, 20, 21]. The clinical expression and severity in Nf1 is diverse, even within families. The complications affect many of the body systems and range from disfigurement, scoliosis and vasculopathy to cognitive impairment and malignancy including peripheral nerve sheath tumours, and central nervous system gliomas. Macrocephaly, short stature and cutaneous angiomas are minor features of the disease [22, 23, 24, 25].

Criteria of National Institute of Health Consensus Development Conference for diagnosis of NF1 [26]. Two or more criteria are needed for diagnosis:

- * Six or more cafe au lait patches >15 mm in adults and > 5 mm in children
- * Two or more neurofibromas or one plexiform neurofibroma
- * Axillary or groin freckling
- * Lisch nodules (iris hamartomas)
- * Optic pathway glioma
- * A first degree relative with NF1
- * A distinctive osseous lesion such as sphenoid wing dysplasia or thinning of the long bone cortex with or without pseudoarthrosis.

Conclusion

Different associations of MDM and NF1 with other genetic diseases were described in literature: coexistence of MDM and congenital cataract, MDM and hyperpigmented spots, MDM and melanoma [36, 37, 38, 39].

Neurofibromatosis, gigantism, elephantiasis neurotomatosa and recurrent massive subperiosteal hematoma etc. [40]. But to the best of our knowledge this is a first description of coexistence of MDM and neurofibromatosis type 1.

Significant improvement was obtained by using a combination of systemic therapy with 13-cis-retinoic acid topical agents (salicylic acid 10 %, emollient with methyluracil and chloramfenicol on fissures). Further investigations to confirm the efficacy of 13-cis-retinoic acid in systemic therapy of MDM are needed but it is difficult due to rarity of this disease.

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