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ORIGINAL RESEARCH— OTOLOGY AND NEUROTOLOGY

Melkersson-Rosenthal syndrome

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OBJECTIVES: To study characteristics of Melkersson-Rosenthal syndrome (MRS) patients with facial palsy (FP) and differences in patients treated at the Departments of Otorhinolaryngology and Dermatology.

METHODS: Clinical picture of MRS was studied from patient charts at two departments. Patients with FP received a questionnaire and were examined. Tissue biopsies were searched for non-necrotizing granulomatous infiltrations typical of MRS and blood DNA for UNC-93B1 gene mutations predisposing to herpesvirus infection.

RESULTS: At the Department of Otorhinolaryngology, all 18 MRS patients had FP, 9 the triad form. Two patients revealed non-necrotizing granulomatous infiltrations during acute edema episodes; another two had association with uveitis. Edema was rarely persistent and did not dominate the clinical picture. No UNC-93B1 mutations were found. At the Department of Dermatology, 2 patients had triad MRS and 15 had monosymptomatic granulomatous cheilitis with persistent edema and typical MRS histology.

CONCLUSION: The clinical picture of MRS with FP differed from the current knowledge of edema-dominated MRS. More studies focusing on MRS with FP would broaden our understanding of the syndrome.

Melkersson-Rosenthal syndrome (MRS) is a rare disorder of unknown etiology, undefined incidence, and inconsistent classification. MRS is classically defined as a triad of recurrent orofacial edema, recurrent peripheral facial palsy (FP), and fissured tongue (lingua plicata, LP).[1] All three symptoms are present in a minority of patients. When two symptoms appear, the form is oligosymptomatic,[1,2] and many investigators consider cheilitis granulomatosa (CG), an intermittent labial or orofacial edema, as a monosymptomatic MRS form.[1,3] This interpretation results from histopathological biopsy findings of edematous tissues in CG and in some other MRS patients being identical, ie, showing non-necrotizing lymphoepitheloid granulomas.[1,3] Some investigators suggest that these two are separate diseases because the majority of CG patients never present with other MRS symptoms.[4]

Most MRS studies are conducted at departments of dermatology or oral and plastic surgery and comprise patients with monosymptomatic CG or oligosymptomatic forms of MRS in which the leading clinical symptom is edema. Few publications present more than one or two patients with the triad MRS form.[1,3,5,6] Studies on patients with FP and fissured tongue without facial edema are very rare and some investigators do not include these patients in MRS at all.[7] MRS patients with FP and without problematic edema have, in general, received little attention.

In conducting the study at the Department of Otorhinolaryngology (depORL), we assumed that most MRS patients would have a history of FP. Previous studies have shown that the predominant manifestation and the most important diagnostic feature of MRS is facial edema[1,3,5,6]; however, this finding may lack relevance for our patients, and we hypothesized that it might stem from the bias of different specialties. Edema is also supposed to affect almost all patients and to progress and become persistent over time.[1,3] We hypothesized that in our MRS patients with FP, progression of the disease would not be observed. This view was based on the fact that such patients seldom need follow-up in our department. We also searched patient charts at the Department of Dermatology (depDerma) to determine whether MRS patients treated in these two departments would vary in their forms of MRS. The etiology of MRS is unknown and herpesviruses have been suggested in MRS as well as in Bell's palsy.[8] We sought possible susceptibility to herpes simplex virus-1 (HSV-1) infections by determining autosomal recessive single-gene mutations leading to intracellular UNC-93B protein deficiency. Such a deficiency impairs cellular interferon antiviral responses to HSV-1 but does not compromise immunity to other pathogens.[9]

METHODS

A computer search of patient records for MRS (diagnosis code G51.2 according to the international statistical classification of diseases and related health problems, ICD) was performed from January 1, 1996 to June 30, 2007 at depDerma and depORL. LP was defined according to Axell[10]

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Table 1
Additional episodic symptoms in 17 patients responding to the Melkersson-Rosenthal syndrome study questionnaire

Additional symptoms	Number of patients (%)
Migraine	8 (47)
Headaches other than migraine	10 (59)
Tinnitus	6 (35)
Sudden deafness	1 (6)
Dizziness	10 (59)
Dry mouth	7 (41)
Contractions or weaknesses of facial muscle	5 (29)
Facial dysesthesia or pain	6 (35)
Dysphagia	5 (29)
Excessive facial sweating	1 (6)
Facial anhidrosis	0
Dry eyes	5 (29)
Disturbances of vision	5 (29)
Excessive tearing	4 (24)

as the dorsum or margins of the tongue being crossed by one or several grooves, estimated to be at least 2 mm deep over a minimum total length of 15 mm. If there was any doubt in patient charts about the LP, severity was considered moderate and not recorded as real LP.

Patients with a history of FP received a questionnaire by mail. They were asked about the time of onset, side, and number of FPs; about the location, duration, frequency, and persistence of facial edema; and about the existence of edemas in other body parts. They were asked whether any relatives had FP, edemas, or fissured tongue and were questioned about additional symptoms (Table 1). They were asked about allergies, any other diseases, medications, and gastrointestinal symptoms. Finally, they were invited to a clinical examination. If the patient had LP, the tongue was photographed (Fig 1). Facial function was assessed by the House-Brackmann[11] and Sunnybrook[12] facial grading systems. A tissue sample (lip, cheek, or tongue) was taken with a 4-mm biopsy punch (in cheek and lip from inside the mouth deep to the underlying muscle) for possible granulomatous infiltration diagnosis. The samples were fixed in formalin. Paraffin-embedded samples were then cut and stained with hematoxylin-eosin and periodic acid-Schiff. The slides were examined by a dermatopathologist. A blood sample was drawn for genetic testing from 13 patients. The samples were stored at −20°C until further use. Genomic DNA was isolated using QiaAmp DNA blood mini kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Mutation (c.1034del4 and c.781G>A) locations in chromosome 11q13 for gene UNC-93B1 were amplified in two distinct reactions with specific primers using AmpliTaq Gold polymerase enzyme (Applied Biosystems, Foster City, CA). Polymerase chain reaction products were purified by QIAquick Gel Extraction Kit (Qiagen) and sequenced.

The study protocol was approved by the Helsinki University Central Hospital Ethics Committee. All patients taking part by questionnaire or examinations gave their written informed consent. The funding source had only a financial role in the study.

RESULTS

The study comprised 35 patients; the computer search yielded 26 patients and an additional 9 patients were found by the authors or with help from colleagues. There were 23 women and 12 men. In depDerma, all 17 patients had labial or facial edema as their most frequent or persistent symptom (Table 2). Samples from edematous tissues, taken for diagnostic purposes, had shown lymphocyte clusters surrounding small vessels in 3 patients and non-necrotizing granulomatous infiltrations typical of MRS in 14 patients. Two of these patients with granulomas also had FP and LP (Table 3, patients 1 and 2), hence a complete triad form of MRS. The remaining 15 patients had CG as a monosymptomatic form of MRS. One of the CG patients had Crohn's disease.

All 18 patients in depORL had FP (Tables 2 and 3, patients 3–20). A full triad of symptoms could be seen in nine patients (Table 3, patients 3, 5–12). Five patients had FP with edema (Table 3, patients 4, 13–16), one had FPs with LP (Table 3, patient 17), and one had an episode of FP with LP and several additional symptoms (Table 3, patient 18) (Table 1). One patient had had FP four times and recurring tears and blisters of the mucous membranes of the mouth (Table 3, patient 19). Herpes infection or MRS was

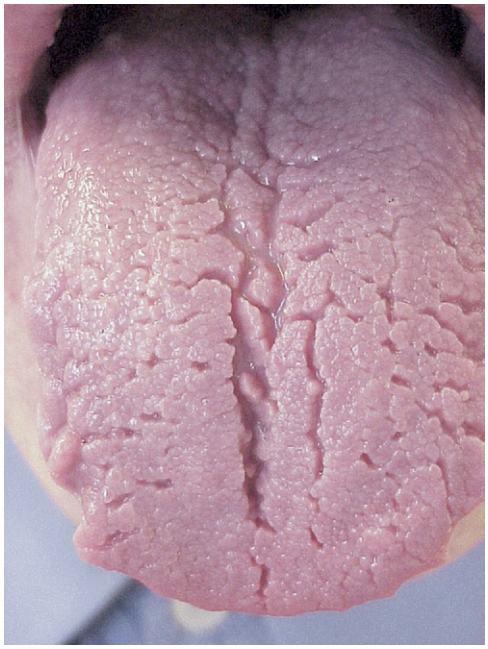

Figure 1 Plicated tongue.