

Immunological study of Melkersson-Rosenthal syndrome. Lack of response to food additive challenge

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Summary

A study was made of six patients with Melkersson-Rosenthal syndrome (MRS) to establish the aetiological role of foodstuffs and/or additives and the possible associated immunological alterations. In all cases Melkersson-Rosenthal syndrome (MRS) was diagnosed both clinically and histologically, excluding other causes of orofacial granulomatosis (OFG). A detailed study of possible triggering factors was performed in all patients. Blood analysis, x-rays and cultures, were always within normal limits, with the exception of the finding of circulating immune complexes (CICs) in three patients with facial palsy associated, and C-reactive protein positivity in two patients who presented persistent labial oedema. All patients were subjected to skin-prick tests with common inhalant allergens and with foods when sensitization to foods were suspected, and patch tests with European Standard Series and pastry components, organic dyes, perfumes and fragrances series. The results were negative in all cases. When asymptomatic, the patients were subjected to a double-blind oral challenge, under placebo control, with additives (monosodium glutamate, tartrazine, sulfites, erythrosine, paraoxybenzoate, sodium benzoate, lactose, aspirin, and annate), which was again negative. In no case did the patients refer the appearance of outbreaks with exposure to foods or contactants, and the course of the disease was unaffected by exclusion diets and the elimination of contactants. To conclude, we observed no sensitization to foods, additives or contactants in our patients. Likewise, there were no antecedents of atopy or hereditary predisposition related to the aetiopathogeny of MRS. The significance of the CIC encountered only in patients with facial paralysis remains to be established, due to the limited number of patients studied.

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Introduction

Melkersson-Rosenthal syndrome (MRS) is an infrequent disease characterized by the association of recurrent or persistent orofacial oedema habitually located in the lips, peripheral facial paralysis and a lingua plicata [1–4].

Labial oedema is the most common and characteristic sign in MRS. Its histopathological study reveals the existence of non-caseous lympho-epithelial and giant cell granulomas identical to those observed in

Miescher's granulomatous cheilitis — currently regarded by most authors as being a monosymptomatic form of MRS [2,5–8] — and similar to those seen in the orofacial manifestations of Crohn's disease and sarcoidosis [7,9,10]. The differential diagnosis of MRS is to be established with these pathologies. In 1985 Weisenfeld *et al.* [11] introduced the concept of orofacial granulomatosis (OFG) to group those processes involving persistent oedema of the lips and adjacent orofacial regions, and whose histological examination reveals non-caseous tuberculoid granulomas.

The aetiopathogeny of MRS is unknown [1,4,7], although infectious mechanisms have been suggested

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[6,7], acting on hereditary factors [12–14], as well as immunological causes [2,15]. The presence of an immunological mechanism is supported by the typical histology of the lesions (hypersensitivity granuloma) [2,7,15]. Moreover, a number of authors have reported patients sensitized to additives and/or foods [16–19] whose identification and dietary suppression leads to a modified evolution in the disease and, in some cases, to the remission of symptoms. The syndrome is reportedly also more common among atopic patients [16,19]. The aim of the present study was to establish the aetiological role of foods and additives in MRS and to evaluate possible immunological alterations.

Materials and methods

Six patients with MRS (five women and one man; age range 38–51 years of age) were studied during 1991. Diagnostic criteria were the presence of recurrent of persistent lip oedema, with typical histology and exclusion of other known causes of orofacial granulomatosis. The syndrome was complete (MRSc): orofacial oedema, lingua plicata and facial palsy, in three cases (cases 1, 2 and 3); and incomplete (MRSi): orofacial oedema with or without lingua plicata, in the remaining three (cases 4, 5 and 6).

The clinical characteristics of the patients are indicated in Table 1. The rest of the physical explorations were normal. The swollen lip was biopsied in all cases, and the histology evaluated after haematoxylin-eosin staining.

History taking was performed to identify possible triggering factors such as foods; additives in food processing and cosmetics or toothpastes, etc.; drugs; physical factors including cold, sunlight and physical exercise; and infection (herpes, influenza, *streptococcus*, oral sepsis, etc).

Dietary habits were also studied, along with work-related factors, hobbies and exposure to contactants, personal or family antecedents of atopy, eczemas, immunodeficiencies, autoimmune diseases and family antecedents of MRS.

Complementary investigations included: haemogram, globular sedimentation rate, biochemistry with proteinogram, coagulation tests, urine analysis, chest x-rays, orthopantomography, pharyngeal swabbing and microbiological culture of other oral septic foci when present, immunoglobulin quantification, complement, C-reactive protein (CRP), antistreptolysin (ASLO), rheumatoid factor (RF), circulating immunocomplexes (CICs, were measured by CIq binding assay), autoantibodies, lymphocyte subpopulations (CD4, CD8), and the study of cellular immunity by intradermal skin tests with a screening panel antigens (tuberculin, candida, mumps, streptokinase, streptodornase and tetanus toxoid) [20].

Allergy study included skin-prick tests with the aeroallergens commonly encountered in our environment: mites, epithelia, fungi, pollens (Alergia e Inmunología Abelló SA, Madrid, Spain), and with foods (CBF-Leti, Barcelona, Spain) when indicated by the clinical history of the patient, and patch tests with European Standard Series (ESS), perfumes and fragrances, pastry components and organic dyes (Marti Tor, Barcelona, Spain) series (Table 2). These series were chosen because they include most of the contactants related to MRS in the literature.

A double-blind oral challenge with additive capsules was carried out (monosodium glutamate 300 mg, tartrazine 30 mg, sulfites 90 mg, erythrosine 15 mg, paraoxibenzoate 250 mg, sodium benzoate 250 mg, lactose 100 mg, acetyl salicylic acid 360 mg, annate 15 mg) under placebo control (talc 100 mg). Intervals of no less than 72 h were spaced between the oral challenges.

Table 1. Clinical characteristics

Case	Age	Sex	Lip oedema				Facial palsy			LP
			AO	No	DUR	PER	AO	Nt	PER	
1	38	F	36	7	6	Yes	23	3	No	Yes
2	39	F	37	24	2	No	19	4	Yes	Yes
3	51	M	48	6	7	No	20	2	Yes	Yes
4	50*	F	48	12	6	Yes		Absent		Yes
5	41	F	38	9	3	Yes		Absent		No
6	38#	F	37	4	3	No		Absent		Yes

* Periodontal disease. #Cluster headache. AO. Age at onset. No. Yearly number of episodes of lip tumefaction. Nt. Number of episodes of facial paralysis. DUR. Outbreak duration (days). PER. Persistence. LP. Lingua plicata.

In those patients in whom the lip condition resolved entirely (cases 2, 3 and 6) the oral challenges were performed in asymptomatic periods. In the other three patients (cases 1, 4 and 5) with persistent oedema between outbreaks, a basic diet was given for 1 month (chicken and veal, cereals, fruit and vegetables, white fish), and contactants were suppressed (i.e. cosmetics, toothpaste, etc.), in an attempt to secure clinical improvement before oral challenging.

The evaluation of response to pharmacological treatment involved the administration of terfenadine (120 mg/day) and prednisone (1 mg/kg/day) for 30 days during lip tumefaction. Prednisone dosing was subsequently decreased until its complete discontinuation after a further 30 days. Two months after testing oral treatment, the three patients with persistent lip oedema received two doses of triamcinolone acetonide (40 mg) intralabially, with an interval of 20 days.

Results

Women clearly predominated in our series (five women and one man). Mean age was 42 years, while age at the onset of lip oedema ranged between 36 and 48 years

(mean 37 years). Half of our cases presented with MRSc, and in these facial paralysis preceded the appearance of lip oedema by several years (range 13–28). One case with oligosymptomatic presentation (case 6) suffered from cluster headaches which again preceded lip oedema by several months. Lingua plicata was present in five cases.

Histopathology revealed non-caseous tuberculous granulomas in two patients, and a predominantly perivascular mononuclear inflammatory infiltrate (lymphocytes, histiocytes and plasma cells) in the other four. The exclusion of other causes of OFG was based on the clinical history and results of the complementary investigations.

Only one patient (case 4) exhibited periodontal pathology, whose treatment failed to alter the course of the disease. No infectious foci were detected in any case. In two families (cases 1 and 4) two first-degree relatives presented lingua plicata, without further signs of MRSc. There were no personal or family antecedents of atopy, and no apparent relationship between the clinical history and possible triggering factors.

The complementary investigations were normal, with the exception of C-reactive protein positivity in two

Table 2. Patch test series

European standard (%)	Pastry (%)	Organic dyes (%)	Fragrance mix (%)
Potassium Dichromate 0.5	Benzoic Acid 5	p-aminoazobenzene 0.25	Cinnamic alcohol 1
Neomycin Sulphate 20	Sorbic Acid 2	p-aminophenol 2	Amylcinnamic aldehyde 1
Thiuram Mix 1	Anethole 2	Disperse blue 3 (Cl. 61505) 1	Cinnamic aldehyde 1
Paraphenylenediamine 1	Persulfate ammonium 2	Disperse orange (Cl. 11080) 1	Salicylic aldehyde 2
Cobalt Chloride 1	Benzoyl peroxide 1	Disperse red 1 (Cl. 11110) 1	Benzyl cinnamate 5
Benzocaine 5	Butyl hydroxytoluene 2	Disperse red 17 (Cl. 11210) 1	Benzyl salicylate 1
Formaldehyde 1	Menthol 1	Disperse Yellow 3 (Cl. 11855) 1	Benzaldehyde 5
Colophony 20	Octyl galete 1	Eosine 50	Eugenol 1
Quinoline mix 6	Sodium benzoate 5		Geraniol 1
Balsam of Peru 25			Hydroxycitronellal 1
PPD-Black rubber mix 0.6			Isoeugenol 1
Wood alcohols 30			Oakmoss absolute 1
Mercapto mix 2			Vanilla 10
Epoxy resin 1			
Paraben mix 15			
BPF-resin 1			
Fragrance mix 8			
Ethylenediamine dihydrochloride 1			
Quaternium 15 1			
Nickel Sulphate 5			
Isothiazolin-3-one 0.01			
Mercaptobenzothiazole 2			
Primin 0.01			

patients with MRSi and persistent oedema (cases 4 and 5), and the detection of circulating immune complexes in three cases with MRSc.

The skin-prick tests with routine aeroallergens were negative. Only one patient associated a possible increase in lip oedema with the eating of nuts, although on other occasions this failed to cause increased tumefaction. Again, skin-prick tests with almonds, hazelnuts, walnut, cocoa, sunflower seeds (CBF-Leti, Barcelona, Spain), were negative, as were the corresponding oral challenges. IgE levels were under 50 IU/ml in four patients and between 250 and 300 IU/ml in the other two. Both the patch tests and the oral challenges with additives were negative in all cases. In the three patients with persistent slight lip oedema between outbreaks, no noticeable decrease in tumefaction was noted with the basic diet or on suppressing contactants. Again, no exacerbation was detected on challenging with additives. The duration and frequency of the outbreaks of lip oedema were not modified by antihistamine (terfenadine) or oral corticoids. The intralesional injection of glucocorticoids only diminished the oedema in one patient (case 1).

Discussion

Melkersson-Rosenthal syndrome generally appears in the second to fourth decade of life, and reportedly affects both sexes equally [1,7]. Mean age in our series coincides with that reported elsewhere. However, a clear female predominance was observed in our study and by other authors [21]. Interestingly, most of the cases reported in Spain correspond to women [21–23]. MRS is an infrequent pathology, without racial predominances [6,7,14,23], although most cases have been reported in northern Europe [1,12,17,19]. In our opinion, these discrepancies may be the result of a lack of uniform criteria in diagnosing MRS.

At present, most authors agree that a definite diagnosis of MRS requires the presence of oedematous lip or facial lesions with characteristic histological features, i.e. non-caseous lymphoepithelial and giant cell granulomas. However, it is more common to find a predominantly perivascular infiltrate consisting of lymphocytes, histiocytes and plasma cells, which represent early stages in granuloma development [1]; as the histopathology in our series revealed. Both Crohn's disease and sarcoidosis may be easily excluded in our study based on the clinical history and results of the complementary investigations.

One half of our patients presented complete MRS. This complete triad presentation is reported in 18–70% of all cases [1], although most authors agree that oligosymptomatic presentations are more common.

These discrepancies may be due to the fact that it is easier to suspect diagnosis in the presence of the classical triad.

Three of our patients suffered episodes of facial paralysis years before the onset of oedema. Facial paralysis may precede or follow the appearance of tumefaction by months or years, or develop concomitantly [7]. One of our patients suffered cluster headaches, a characteristic also associated with MRS [1], along with other neurological and mucocutaneous manifestations [6,7,24].

The literature presents a great variety of results as regards response to pharmacological treatment with glucocorticoids, danazol, clofazimine, sulfones, salazosulfapyridine, and methotrexate [4–7,22,25,26]. Some authors have even reported good responses with terfenadine [19]. In our study both oral glucocorticoids and antihistamines (terfenadine) were of little use, although the intralesional injection of corticoids did reduce lip oedema in one case.

A number of workers have suggested a fundamentally viral infectious origin in MRS, and a relation to chronic periodontal infections [6,7]. In our series only one patient suffered periodontal disease, and treatment of the latter failed to alter the course of the syndrome. No infectious foci could be established in the remaining patients.

Many cases of familial MRS have been reported, and an autosomal dominant hereditary mechanism has been proposed [13]. Lingua plicata is an autosomal dominant hereditary condition with an incidence of 0.9–15% among the general population. However, its frequency reaches 62–77% in MRS [4,13]. In our series in two families (33%) there were two members with lingua plicata, but we did not consider the isolated presence of lingual plicata to constitute a sign of MRS.

The complementary investigations in the present study yielded normal results, with the exception of C-reactive protein positivity in the two patients with incomplete MRS and persistent oedema, and the presence of CICs in the three cases with complete MRS. The clinical significance of these findings is not clear, due to the few cases studied. No known marker for MRS is known; complementary investigations tend to be normal or else reflect a slight inflammation in the form of an elevated sedimentation rate, and raised gammaglobulins and IgG and IgA fraction [7]. Although occasional reports have been published of MRS associated with rhinitis and allergic asthma [16,23] and a number of authors have suggested that the syndrome is more frequent among atopic individuals due to the existence of an altered cell-mediated immune response [16], most series report no relation to atopy [1,4,6,9,21]. None of our patients had personal or family antecedents of atopy, and no sensitization to aeroallergens could be demonstrated. The total

serum IgE levels were within normal range in our environment [27,28].

A number of authors have also reported that certain MRS patients exhibit sensitization or intolerance to additives, foods or contactants that may be linked to the syndrome outbreaks. However, these are usually isolated cases [16–18] in which the cause-effect relationship is not always clear. In our patients we were unable to demonstrate intolerance or allergy to contactants, additives or foods.

In conclusion, the aetiopathogenia of MRS remains uncertain, although the histology of the lesions suggests the participation of a type IV immune mechanism. In our patients we were unable to demonstrate allergy to additives or foods, and no elevated incidence of atopy. These findings agree with those reported by most authors. No family antecedents of MRS were noted, as the isolated presence of lingua plicata was not regarded a sign of MRS.

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