

Family Study on Melkersson–Rosenthal Syndrome

Some Hereditary Aspects of the Disease and Review of Literature

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The medical records of 73 unrelated patients with either complete or incomplete Melkersson–Rosenthal syndrome attending our department between 1967 and 1985 were analyzed, and 42 of them as well as 171 of their relatives were examined. Lingua plicata was seen in 10, and other features were detected in 6 of the 42 families. The limited frequency of signs characteristic for the syndrome in the relatives examined suggest a multifactorial origin including a genetic basis. **Key words: Clinical criteria; Multifactorial causality.**

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First described by Melkersson (1) and further characterized as a clinical entity by Rosenthal (2) a number of authors have discussed whether or not the now termed Melkersson–Rosenthal syndrome (MRS) is a hereditary affliction (2–23). That this question is still open is due to the lack of large-scale genetic investigations and the vexing variety of major and minor clinical manifestations of MRS with different signs in often varying combinations. The featuring triad of recurrent labial edema, peripheral facial palsy and plicated tongue is often combined with additional nerve, eye, vasomotor and sialogland oro-facial symptoms (8, 9). Abortive forms of MRS outnumber the classical triad form (9).

Abnormal reactivity of the cranial neurovascular system causing intermittent orofacial edema is suspected etiologically in MRS (8, 9). Hence the regional mucocutaneous conditions may be more susceptible to mild inflammatory reactions to noxious (allergenic and/or infectious?) agents (9). The histology of small perivascular tuberculoid granulomas sparsely scattered in the edematous tissue (Miescher's cheilitis granulomatosa) supports this concept (9). However, a definite provenance of this oligogranulomatous inflammation pattern has not yet been found.

No systematic study of family cases of MRS has yet

been made, although since the 1930s quite a number of such cases have been reported, suggesting a genetic origin of MRS (2–23). Hence, the aim of this study was to investigate the genetic aspects of the disease by examining a large number of MRS patients and their relatives. The presence of MRS features in some of the first- and second-degree relatives could be shown. First-degree relatives included parents, siblings and children, and second-degree relatives, grandparents, siblings of the parents and nephews and nieces of the patient. To exclude a pure infectious origin of MRS, marital spouses have also been examined.

MATERIAL AND METHODS

MRS patients and their families

From 1968 to 1985, 73 (28 male, 45 female) unrelated patients with different manifestations of MRS were treated in the Erlangen Department of Dermatology. Ages at onset of disease ranged between 6 and 66 years.

Re-examination was offered to all patients and their family members. Forty-two out of 73 patients and 171 members of their nuclear families could be reached and examined once or several times (Tables I and II). The medical history, the neurological and dermatological status of all 42 available index patients and their relatives were carefully checked with particular reference to any signs of MRS. Using major and minor criteria of MRS [combining histology and the totality of chief and marginal clinical manifestations as published elsewhere (9)], we classified our sample of patients, dividing them into complete and incomplete forms of MRS. The incomplete form of MRS was subgrouped into A (confirmed MRS), B (probable MRS), C (uncertain MRS) and D (unsettled).

Major criteria of MRS include painless relapsing oro-facial edema with epithelioid cell histology of type 'cheilitis granulomatosa' (ch.gr.), peripheral facial palsy (f.p.), plicated tongue (l.pl.), transitory disorders of CNS and craniocervical nerve disturbances other than facial nerve.

Minor criteria include typical oro-facial edema without confirmatory histology, premonitory and migraine-like cephalgia, transient salivary, lacrimal and pupillomotoric dysfunctions (for details, ref. to 9).

Migraine-like headache in patients with MRS was mentioned early by Rosenthal (2). About 40% of our MRS patients complained of this symptom, characterized by sudden occipital or frontal cluster headache without nausea.

Pedigrees of the families with MRS signs in family members detected from the sample participant in that study

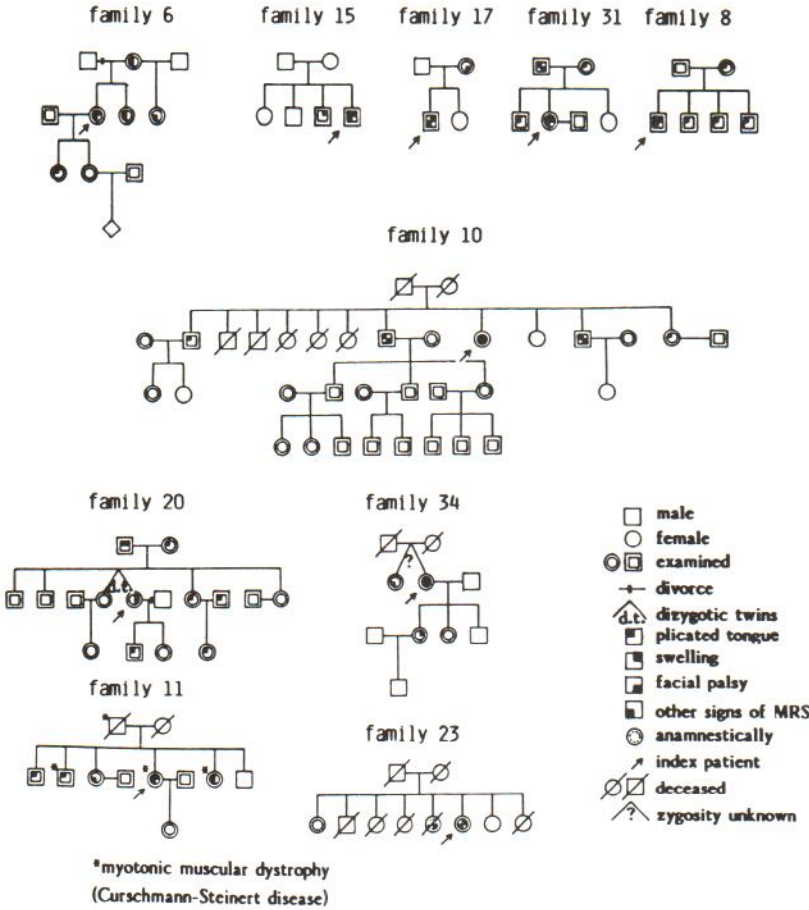


Fig. 1. Pedigrees of the 10 families with signs of MRS detected in members participating in this study.

RESULTS

Our family explorations did not reveal consanguinity among the ancestors of the MRS patients examined. Cases of complete MRS could not be found either in the families of the re-examined patients or in the clinical files of those patients not available for re-examination. In 10 families, however, several disorders compatible with MRS were observed in I° relatives. Details of the pedigrees are shown in Fig. 1.

Facial palsy in I° relatives

In family 10, 2 brothers among 5 living siblings of the MRS patient (60y/f, with f.p., l.pl., labial edema and cluster headache) suffered from recurrent mild unilateral peripheral palsy.

The mother of the MRS patient (20y/m) in family 17 reported f.p. persisting for 6 months, 20 years ago. However, medical examination revealed neither traces of f.p. nor other signs of MRS.

Table I. Index patients with MRS re-examined

	Participant	Non-participant		
		Died	Refused	Could not be traced
Male	11	6	1	10
Female	31	-	1	13
Total	42	6	2	23

Table II. Index patients with MRS and their relatives examined

	Male	Female	Total
MRS patient	11	31	42
I° relatives	44	44	88
II° relatives	17	20	37
Marital spouses	26	20	46
Total	98	115	213

In family 23, one sister (out of 8 siblings) of the MRS patient (60y/f, suffering from recurrent lip edema and cluster headache) had been affected by f.p. at age 26. Since she died one year later after childbirth, the cause of her f.p. remained obscure.

Facial swellings in I° relatives

In family 15, one brother (out of 3 siblings) of the MRS patient (35y/m, suffering from recurrent facial edema since age 22, cluster headache, bouts of dizziness and hyperlacrimation) complained of episodic labial swellings and paradox hyperlacrimation.

The father of the MRS patient (40y/f) in family 20 showed remarkable l.pl. and suffering from bouts of painless upper lip edema. The neurological state of either patient was normal.

The twin sister (zygosity undetermined) of the MRS patient (61y/f, full-blown MRS) in family 34 mentioned repeated psychiatric therapy yet refused to give detailed information. She denied f.p., cephalgia or muco-cutaneous swellings and declined medical examination. One daughter among 3 children of the MRS patient showed transient lip swellings in the morning hours, allegedly triggered by emotional stress.

Lingua plicata in I° relatives

Lingua plicata (l.pl.) was observed in 62% of the MRS patients, 36% in I° relatives, 5% in II° relatives and 11% in the marital spouses examined. However, l.pl. in more than 3 relatives was found only in 6 families (nos. 6, 8, 10, 11, 20, 31). Excluding those families with l.pl. as the sole MRS sign from the MRS group, l.pl. was seen only in 14% of I° relatives. The low frequency of l.pl. in II° relatives could be due to the limited number of cases available for examination ($n=37$).

Table III. Case reports of MRS including medical examination of family members

First author	Year	Family members with observed signs of MRS	Families with features of MRS	Families examined
Alexander	1972	2	1	1
Asada	1966	2	1	1
Boeri	1969	2 ^b	1	1
Carr	1965	3	1	1
Kissel	1976	5	1	1
Kunstadter	1965	3	1	1
Lygidakis	1979	9	1	1
Midana	1958	5	1	1
Nally	1970	3	1	1
Rossolimo ^a	1901	3	1	1
Scott	1964	4	1	1
Terespolsky	1970	2	1	3
		2	1	
		3	1	
Tosti	1968	3 ^c	1	1
Vakato	1960	6	1	1
Wessels	1979	2 ^b	1	1
Total		59	17	17

^a Probable MRS.

^b Concordant monozygotic twins.

^c Dizygotic twins.

Additional nosological findings

In family 11, hereditary myotonic dystrophy (Curschmann-Steinert's disease, unrelated to MRS) was detected in the MRS patient and in 2 of her 5 siblings.

DISCUSSION

Reports of MRS cases in families date back to the 1930s. The available data include examined cases (two or more) of MRS within single families (Table III) as well as case reports only through family history (Table IV). The latter statements indicate variably expressed traits of probable inheritance in some patients suffering from MRS.

When l.pl. was considered a constitutive sign of MRS in such cases (Table III), 59 relatives in 17 families could be classified as MRS patients. If we regard the l.pl., known to be inherited as an autosomal dominant trait (13), as not being associated with MRS, the number of family members with MRS decreases to 38.

Traced from reported family histories of MRS pa-

Table IV. Clinical studies of MRS including family histories of patients (without clinical examination of family members)

First author	Year	Family members with reported signs of MRS	Families with features of MRS	Family histories analysed
Ekbohm	1950	4	2	8
Hornstein	1962	6	3	62
Kettel	1959	4	2	13
New	1933	2	1	67
Rosenthal	1931	10	3	4
Worsaae	1982	6	3	33
Total		32	14	187

tients, 32 members out of 14/187 families could be found with several signs suggestive of MRS (Table IV). L.pl. was not mentioned in these family reports. It should be emphasized that some neurological disorders clearly independent of MRS (e.g., sequelae of cerebral stroke) may in the absence of personal examination, be mistaken for signs of MRS.

As expected, the MRS incidence in examined cases (in literature, Table III, including l.pl. as sign of MRS) was higher than in our patients, in family histories (Table IV, l.pl. not considered) lower than in our sample.

In the present family study the full-blown spectrum of major criteria for complete MRS could not be found either in any relative of the MRS patients re-examined ($n=42$) or in the family histories of the remaining patients not available ($n=31$). There are few reports of complete MRS (with or without typical histology) in one or more family members (2, 4, 5, 18).

Cases of complete so-called 'classical' MRS obviously represent a minor proportion within the wide range of clinical manifestations consistent with MRS (8, 9). This is in accordance with the updated Erlangen sample (9). Individuals reporting and suffering from only a few clinical signs otherwise typical of MRS may represent an 'incomplete' expression of the disease.

The prevalence rates reported by Zülch (24) for f.p. of a different origin and in a German population, estimated by Gottwald to be $<1\%$ (personal communication), are significantly lower than in our sample of I° relatives ($\approx 3.5\%$). Additionally, searching for f.p. in the files of 25 743 patients hospitalized be-

tween 1970 and 1982 at our Department, only 42 cases ($\approx 0.16\%$) of f.p. could be found. Nine of these cases were due to acute zoster oticus, one to sequelae of congenital syphilis, 7 to former trauma, and 25 were associated with MRS.

If one considers solitary l.pl. to be a minor criterion of MRS, a family incidence of MRS is noted in 10/42 of our families studied ($\approx 24\%$). If we disregard solely existing l.pl. as a sign of MRS, only 6 families ($\approx 14\%$) with cases of MRS remain.

It should be mentioned that l.pl. of different degree was observed in 26 out of 42 MRS patients re-examined ($\approx 62\%$). In a prospective study of 4 533 unselected individuals attending our outpatient clinic in 1981, we found an incidence of l.pl. in 15% of the sample examined (unpublished data).

Some authors have assumed an autosomal dominant inheritance of MRS, due to several case reports suggesting such a genetic trait (2, 6, 12, 13). However, neither the risk for I° relatives estimated by family histories of MRS cases ($\approx 7\%$) nor the results of the present family study lend support to this opinion. If we include I° relatives with solitary l.pl. among those family members showing some other signs typical of MRS, the resulting figure ($\approx 34\%$) would suggest an autosomal dominant trait for MRS with minor phenotypic penetrance. On the other hand, solitary l.pl. of different degree is known as a harmless autosomal dominantly inherited anomaly (13) seen in about 15% of the German population. A highly significant ($p < 0.001$) difference in the prevalence rates of l.pl. is evident in our MRS patients ($\approx 62\%$) as compared with dermatological outpatients free from MRS ($\approx 15\%$). However, it remains doubtful whether the association of a stable hereditary anomaly such as l.pl. with the recurring signs and symptoms of MRS can be regarded as an argument for autosomal dominant inheritance of the syndrome as a whole. Nevertheless, the striking connection of l.pl. with many manifestations of MRS would seem to indicate a peculiar genetic constellation that may have some significance for the phenotypical expression of the syndrome.

Only two pairs of monozygotic twins with typical MRS have been reported so far (5, 22). The twin sisters of 3 of our female MRS patients revealed no clinical signs of MRS. In one twin pair, probably monozygotic (showing identical HLA pattern and physiognomy) in family 34, the sister of the MRS patient suffered from a mental disorder of unknown origin.

Both the results of our family study and the analysis of previous case reports can best be explained by assuming a polygenic propensity for development of MRS. This assumption is based on the following criteria:

no cases of consanguinity were traced or reported on in the ancestry of our MRS patients;
the risk for MRS in I° relatives was estimated in our sample to be 24% with 1.pl. or 8% without 1.pl., resp.;
the risk for MRS in II° relatives was found to drop below 5%.

While cases of full-blown MRS seem to be rather rare, a variety of minor clinical signs typical of incomplete or even complete MRS can also be detected in general population. Intermittent neurovegetative disturbances such as unilateral salivary, lacrimal or vasomotoric oro-facial dysfunctions may be due to different causes and may occur either solitarily or in familial clusters. So it is hardly possible to prove a common hereditary or non-hereditary denominator for those recurrent disorders.

Well documented cases of family occurrences, two additional reports on monozygotic twins with MRS, and the risk rates established in this study for signs of MRS in I° relatives of MRS patients all lend support to the concept of a genetic basis predisposing toward the syndrome. Moreover, the frequent linkage of 1.pl. with other signs of MRS denotes a particular hereditary background possibly important for intrinsic conditions making possible clinical manifestations of the syndrome.

In an immunogenetic study on the HLA pattern in MRS, recently performed with 27 patients and 46 of their I° relatives in the same sample, we found remarkable yet statistically non-significant frequencies of HLA-B 16 and -Cw3 in comparison with the controls (25). Whether or not these prevalences and, moreover, the absence of the haplotypes HLA-B22, -B 37, -Cw 1 and -DR 9 in the MRS patients may indicate any immunogenetic propensity to manifestations of MRS, remains to be established.

Environmental influences and an increased susceptibility to neurovegetative disturbances due to neuroendocrine or vasomotoric imbalance can enhance a localized allergic reactivity against hidden microbial agents. Even mental distress has been shown to elicit some signs of MRS (9). Hence, considering both earlier reports and the results of the present family study carefully, a multifactorial origin of the syndrome based on a hereditary predisposition appears to be most likely.

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