

Original Article

Retrospective analysis of 69 patients with Melkersson-Rosenthal syndrome in mainland China

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Abstract: Melkersson-Rosenthal syndrome (MRS) is a rare disease with unclear etiology. The clinical manifestations of MRS are characterized by swelling face and lips, peripheral facial paralysis, and fissured tongue. We summarized 69 patients with Melkersson-Rosenthal syndrome in mainland China by searching for PubMed, and Chinese main electronic databases including Chinese National Knowledge Infrastructure Databases (CNKI) and Wanfang. This disease could occur at any age, including teenagers and aged person. 75.4% of patients with typical MRS triad symptoms, while the others only with one or two initial symptoms. Cheilitis granulomatosa is also a type of MRS. No standard diagnostic criteria has been issued to date, and biopsy is generally needed to make a definite diagnosis. Immunosuppressive therapy is of some efficacy in treating MRS; however, no specific treatment has been identified to treat MRS.

Keywords: Melkersson-Rosenthal syndrome, clinical characteristics, treatment

Introduction

Melkersson-Rosenthal syndrome (MRS), also known as recurrent facial palsy syndrome with swelling of the face and lips, is a rare neurological disorder involving skin and mucosal lesions. The etiology of MRS is rather complicated; several factors including genetic and immunologic factors are also involved. The clinical manifestations of MRS are characterized by recurring non-depressive swelling of the face and lips (mainly the upper lip), peripheral facial paralysis, and fissured tongue. Melkersson, a Swiss clinical researcher, firstly noticed intermittent facial paralysis and angioneurotic edema in the lips of a woman in 1928. Shortly after, a German physician, Rosenthal, described fissured tongue in this disorder. However, this disease had not been described as "Melkersson-Rosenthal syndrome" until 1949 [1-4]. MRS is mainly found in teenagers. Most of the reviews that focused on MRS only describe about 2 to 7 patients [2-5], thus the overall features of the patients with MRS could not be sufficiently described, and a more comprehensive study with larger sample size should be performed to further investigate this disorder. In this study,

we summarized the MRS case reported in china mainland.

Method

Literatures searching

We searched several electronic databases including Pubmed, and Chinese National Knowledge Infrastructure Databases (CNKI) and Wanfang, for studies focused on MRS between January 2000 and December 2012. Additional studies were identified by searching reference lists and related citations. The medical subject headings as search terms were used, including "MRS" "Melkersson-Rosenthal syndrome", "Melkersson-Rosenthal syndrome" in Chinese. Searches were limited to medical literature only. Literatures that reported clinical MRS case in china mainland were considered eligible, review literatures or repeated reports were excluded.

Data extraction and statistical analysis

Data of patients with MRS were extracted for each eligible literature including demographic characteristics, onset year, result of tissue

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Table 1. Onset age and symptom of 69 patients with MRS in mainland China

Variables	Total N=69 (100%)	Female N=28 (40.6%)	Male n=41 (59.4%)	<i>P</i>
Diagnosis time (year), median (IQR)	4 (1.5-9)	3 (1.12-9.75)	4 (1.5-9)	0.665
Min	0.01	0.01	0.02	
Max	30	30	27	
Onset age (year), median (IQR)	22 (16-38)	26 (16.5-44.3)	22 (16-37)	0.271
Min	1	9	1	
Max	69	69	69	
Onset symptom, n (%)				0.734
Edema	30 (43.5)	11 (39.3)	19 (46.3)	
Facial paralysis	21 (30.4)	10 (35.7)	11 (26.8)	
Edema + Facial paralysis	10 (14.5)	4 (14.3)	6 (14.6)	
NR ^a	8 (11.6)	3 (10.7)	5 (12.2)	

NR^a, not reported. IQR, interquartile range.

biopsy, clinical symptoms and treatment. SAS 9.3 was used for statistical analysis. Students' t-test or Wilcoxon two-sample test were used for comparison of continuous variable between two groups, chi-square test or fisher exact test were used for comparison of categorical variable among groups. *P*-value <0.05 were considered statistical significance.

Results

General information and clinical symptoms

Data of 69 patients with MRS were extracted from 48 eligible literatures. Among these 69 patients, there were 41 (59.4%) male and 28 (40.6%) female, the median of onset age was 22 years (IQR, 16-38; range, 1 to 69), the median of time from onset age to diagnosis was 4 years (IQR, 1.5-19; range, 0.01 to 30). 43.5% and 30.4% of patients with edema and facial paralysis as onset symptom, respectively, 14.5% of patients' onset symptom were edema along with facial paralysis. There were no differences in diagnosis time, onset age and onset symptom between male and female patients (*P*>0.05), data were showed in **Table 1**.

Clinical symptoms of 69 with MRS were showed in **Table 2**. Among these 69 patients, there were 68 with swelling of the lips and face (including 38 patients with swelling of the lips and cheeks, 22 patients with swelling of the lips, and 8 patients with swelling of the cheeks), 13 with periorbital and eyelid edema, 3 with swelling of the chin, 3 with limb edema, 1 with

swelling of the gum, and 1 with swelling of the nose. Among the 65 patients with peripheral facial paralysis, 40 were with bilateral alternating facial paralysis, and the other 25 were with unilateral facial paralysis. Among the 54 patients with fissured tongue, 5 (7.2%) reported with this manifestation from childhood, and this manifestation was also found in their immediate family members in other 6 (8.7%) patients. Other symptoms including hypogeu-sia (11 patients), facial paresthesia (10 patients), conjunctival congestion (5 patients), paroxysmal headache (1 patient), intermittent facial seizures (1 patient), impaired vision (2 patients), oral ulcer (2 patients), and antiadon-cus (2 patients) were also found. Cranial nerve damages were found in 15 patients, and 8 of them were with glossopharyngeal nerve and vagus nerve involvement.

The typical triad symptom of MRS includes recurring non-depressive swelling of the face and lips (mainly the upper lip), peripheral facial paralysis, and fissured tongue (**Figure 1**). In this study, typical triad symptom of MRS was found in 52 (75.4%) patients, including 33 male patients and 19 female patients. Typical triad symptom was not found in 17 (24.6%) patients, including 3 patients with edema only, 12 edema patients along with facial paralysis, 2 edema patients along with fissured tongue (**Table 2**). There were no differences in diagnosis time, onset age and gender between patients with typical triad symptom or not (*P*>0.05), data were showed in **Table 3**.

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Table 2. Clinical symptom of 69 with MRS in mainland China

Clinical syndrome	Frequency (%)
Edema and swelling	
Swelling of the lips or face	68 (98.6)
<i>Swelling of the lips and cheeks</i>	38 (55.1)
<i>Swelling of the lips</i>	22 (31.9)
<i>Swelling of cheeks</i>	8 (11.6)
Periorbital and eyelid edema	13 (18.8)
Swelling of the chin	3 (4.3)
Limb edema	3 (4.3)
Swelling of the gum	1 (1.4)
Swelling of the nose	1 (1.4)
Peripheral facial paralysis	
Bilateral alternating facial paralysis	40 (58.0)
Unilateral facial paralysis	25 (36.2)
Fissured tongue	54 (78.3)
With fissured tongue from childhood	5 (7.2)
Fissured tongue found in immediate family members	6 (8.7)
Other symptoms	
Hypogeusia	11 (15.9)
Facial paresthesia	10 (14.5)
Conjunctival congestion	5 (7.2)
Paroxysmal headache	1 (1.4)
Intermittent facial seizures	1 (1.4)
Impaired vision	2 (2.9)
Oral ulcer	2 (2.9)
Antiadoncus	2 (2.9)
Cranial nerve damages	15 (21.7)
<i>With glossopharyngeal nerve and vagus nerve involvement</i>	8 (11.6)
Triad symptoms	
Typical triad	52 (75.4)
Without typical triad	17 (24.6)
<i>Edema</i>	3 (4.3)
<i>Edema and facial paralysis</i>	12 (17.4)
<i>Edema and fissured tongue</i>	2 (2.9)

Complications of patients with MRS were showed in **Table 4**, including infection (3 patients, including 2 with herpesvirus infection and 1 with candida albicans infection), keratitis (3 patients), allergic reactions (2 patients), periodontal disease (2 patients), arthritis (2 patients), nasosinusitis (2 patients), pulmonary tuberculosis (2 patients), congenital aortic valve insufficiency (2 patients), facial erythema (1 patient), ulcerative colitis (1 patient), mild anaemia (1 patient), IgA nephropathy (1 patient), Raynaud syndrome (1 patient), vitiligo (1 patient), hyperthyroidism (1 patient), mood disorder

(1 patient), poliomyelitis (1 patient), and lacunar infarction (1 patient) were also reported. Two nodules were found in the upper lip of a patient suggesting sarcoidosis; however, no biopsy was performed for further examination. No Crohn's disease was reported for these 69 patients.

Tissue biopsy

Biopsy was performed in 27 of the 69 patients, pathological changes including non-caseating granulomas in 10 patients (37%), lymphedema in 17 (63%) patients were seen. There were no differences in age and gender between patients with non-caseating granulomas or not ($P>0.05$), data were showed in **Table 5**. The manifestations of the 10 patients with noncaseating granulomas were mainly chronic inflammatory changes, including the infiltration of lymphocytes, macrophages, plasmacytes, histiocytes, and Langhans' giant cells; small amount of monocyte-macrophages and epithelioid cells infiltration was also been found. While for the 17 patients with lymphedema subtype MRS, the manifestations mainly include cellular edema, interstitial edema, lymphangiectasia, and diffuse lymphocytic infiltration; small amount of monocyte-macrophages and epithelioid cells infiltration was also been found.

Treatments

Treatments were reported for 55 patients, including high-dose of methylprednisolone therapy [6], oral intake or injection of prednisone, triamcinolone tablets, dexamethasone, or prednisolone. Vitamins therapy included vitamin B1, B2, B6, B12, C, and E were also used. Fourteen patients were treated with corticosteroids, vitamins, and acupuncture; 6 were



Figure 1. A: An aged patient with swelling of the face and lips, bilateral facial paralysis, and fissured tongue (6); B: A young patient with swelling of the face and lips, peripheral facial paralysis, and fissured tongue, which were confirmed by pathological examinations (7).

Table 3. Comparison between MRS patients with typical triad or not

Variables	Typical triad n=52	Without typical triad n=17	P
Gender			0.232
Female	19 (36.5)	9 (52.7)	
Male	33 (63.5)	8 (47.1)	
Diagnosis time (year), median (IQR)	4 (1.5-10)	3.25 (1.12-6.25)	0.448
Min	0.01	0.02	
Max	30	30	
Onset age (year), median (IQR)	22 (16-37)		0.912
Min	1	1	
Max	69	58	

treated with corticosteroids and methycobal, and 5 were treated with corticosteroids and traditional Chinese medicine, 5 were treated with vitamin only, 15 were treated with vitamin and corticosteroids, treatment and outcome for patients with MRS were showed in **Table 6**. Frequency of complete remission, partial remission and no remission for treatment were 4, 48 and 3, respectively. There was one no remission patient in each subgroup treatment of vitamins only, thalidomide only and corticosteroids + vitamins + acupuncture.

Discussion

The etiologies of MRS are still unclear, and several factors including genetics, infection, aller-

gic responses, immune response, and dysfunction of autonomic nerve are involved in the pathogenesis of MRS. Cockerham suggested that herpesvirus infection is an important inducing factor of MRS, which have been proven by the findings of the present study, of which there were 2 patients with herpesvirus infection [9]. In addition, 1 patient with candida albicans infection was also identified in the present study. Catching a cold could also may be a risk of MRS, which had been dem-

onstrated in a case reported by Li et al. [10]. In that case, swelling and itching of the upper lip, facial paralysis in the left face and intermittent facial seizures, facial paralysis in the right face accompanied with aggravation of upper lip swelling was found in a young male patient at 18, 8, and 1 months before the diagnosis of MRS, which was supposed to be induced by influenza. In the present study, 8 patients were found with swelling lips or unilateral facial paralysis after influenza, which also confirmed the role of influenza in the induction of MRS. Interestingly, 3 patients were found with swelling lips and facial paralysis as their fathers, suggesting genetic factors also play a role in MRS. One patient had eaten a lot of instant

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Table 4. Complications of 69 patients with MRS in mainland China

Complications	Frequen- cy (%)	Complications	Frequen- cy (%)
Infection	3 (4.3)	Ulcerative colitis	1 (1.4)
<i>Herpesvirus infection</i>	2 (2.9)	Mild anaemia	1 (1.4)
<i>Candida albicans infection</i>	1 (1.4)	IgA nephropathy	1 (1.4)
Keratitis	3 (4.3)	Raynaud syndrome	1 (1.4)
Allergic reactions	2 (2.9)	Vitiligo	1 (1.4)
Periodontal disease	2 (2.9)	Hyperthyroidism	1 (1.4)
Arthritis	2 (2.9)	Mood disorders	1 (1.4)
Nasosinusitis	2 (2.9)	Poliomyelitis	1 (1.4)
Pulmonary tuberculosis	2 (2.9)	Lacunar infarction	1 (1.4)
Congenital aortic valve insufficiency	2 (2.9)	Crohn's disease	0 (0.0)
Facial erythema	1 (1.4)		

Table 5. Pathological changes in 27 patients with MRS in mainland China

Variables	Lymphedema n=17	Non-caseating granulomas n=10	P
Gender			1.000
Female	10 (58.8)	6 (60.0)	
Male	7 (41.2)	4 (40.0)	
Age (year), median (IQR)	38 (23.5-46.3)	40.5 (20.8-47.8)	0.880
Min	16	18.5	
Max	69	58.2	

noodles from childhood, and the results of patch test suggesting this patient was allergic to food preservatives; treating with glucocorticoid could effectively improve the swelling of the face and lips, which suggested allergic responses in this patient. In addition, fatigue, drinking, insect bites, bite in the upper lip, and anxious have also been found could induce the swelling of the face and lips as well as facial paralysis.

The pathological features of MRS mainly include tissue edema, noncaseating granulomas with the infiltration of epithelioid cells and Langhans' giant cells, lymphangiectasia, perivascular lymphocyte infiltration, and fibrosis. The pathological types of MRS are generally classified as nodular granuloma- and lymphedema-type. In the present study, biopsy had been performed for 27 patients, and noncaseating granulomas were found in 10 patients and lymphedema in the other 17 patients.

The most commonly found clinical manifestation of MRS is swelling of the face and lips. In

the present study, mostly all the patients were found with swelling of the face and lips. The swellings were mainly acute, painless, and non-depressive swellings, which generally occurred in the lips, especially the upper lip. The initial episode of swelling could recover in several hours to weeks; however, intermittent recurrence of the swelling could occur, which could lead to permanent swelling. The manifestations of MRS are of some

similarities with vascular edema, but the duration of edema is longer and could not be alleviated by antihistamines. Long-term edema could also lead to tissue lesions and induce the development of fibrosis, which could be palpated as hard lesions. For some cases, swellings could also involve eyelids, nose, chin, and limbs. Li reported a boy with the onset of facial paralysis, swellings in the left face and lips, and non-depressive swelling in the bilateral lower-limbs, which had repeated for

3 times [7]. Bilateral alternating of the manifestations was found in this boy. In addition, similar episodes had also been found in the boy's father. No abnormalities were found after experimental and imaging examinations had been performed, and the manifestations were considered as the results of distal vasomotor disorders caused by autonomic nervous system lesions.

Peripheral facial paralysis could occur after the episode of the swelling of the face and lips, or several months or even several years before the swelling of the face and lips. The peripheral facial paralysis could be unilateral, bilateral, or bilateral alternating facial paralysis, which generally occur with the swelling of the face and lips. Facial nerve oppression caused by facial edema has been supposed to play a role in peripheral facial paralysis. In the present study, 65 patients were found with peripheral facial paralysis, and most of them were with bilateral alternating facial paralysis. Hypogeusia in the front two-thirds of the tongue, facial paresthesia, intermittent facial seizures, oral ulcer,

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Table 6. Treatment and outcome for 55 patients with MRS in mainland China

Treatment	Complete remission	Partial remission	No remission	Total
Corticosteroids + vitamins + acupuncture	1	12	1	14
Corticosteroids	1	5	0	6
Corticosteroids + methycobal	0	5	0	5
Corticosteroids + hydroxychloroquine + tripterygium glycosides	0	1	0	1
Corticosteroids + traditional Chinese medicine	0	5	0	5
Methotrexate + traditional Chinese medicine	0	1	0	1
Vitamins	0	4	1	5
Vitamins + corticosteroids	2	13	0	15
Vitamins + tripterygium glycosides	0	1	0	1
Vitamins + traditional Chinese medicine	0	1	0	1
Thalidomide	0	0	1	1
Total	4	48	3	55

impaired vision, conjunctival congestion, paroxysmal headache, and multiple cranial nerve lesions (including optic, oculomotor, trigeminal, facial, auditory, glossopharyngeal, vagus, and hypoglossal nerves). Migraine have also been reported in some cases of MRS, while in the present study, only 1 patient was found with typical migraine although paroxysmal headache had been identified in 4 patients.

Fissured tongue, also known as scrotal tongue, is caused by the abnormal development of the tongue, could also been found in normal subjects. The incidence of fissured tongue in normal population is very low, however, the incidence increase sharply in patients with MRS. Studies have reported that the incidence of fissured tongue is about 30 to 80% in patients with MRS [11]. In the present study, 78% of the included patients were found with fissured tongue. The folds and furrows in the tongue could effectively increase the risk of infection of bacteria and fungus. Hypertrophy of the tongue could be found, which could accompanied with burning pain in some rare cases. Genetic predisposition of fissured tongue has been demonstrated in several studies. In the present study, 9% of the patients were found with fissured tongue from childhood, and fissured tongue was also found in the immediate family members of 11% of the patients.

The diagnosis of MRS is mainly based on the appearance of MRS triad, namely swelling of the face and lips, peripheral facial paralysis, and fissured tongue, in Chinese patients. However, these 3 main symptoms could occur inde-

pendently, and biopsy examinations for noncaseating granulomas are generally needed for the diagnosis of MRS when only 1 or 2 symptoms occur. In the present study, the mean time between the appearance of initial symptom and the diagnosis of MRS was 7 years; while for 2 cases, the time was even as long as 30 years. Therefore, careful reviewing of the medical history, dynamic observation of clinical symptoms and signs, and long term follow-up observations are needed to exclude other potential diseases for patients with atypical symptoms. Elias et al. [8] have suggested that the diagnosis of cranial nerve damages, such as paresthesia in the mouth and face, hearing loss, pharyngeal neuralgia, and pharyngospasm, could help the diagnosis of MRS. Ozgursoy also suggested that for patients with recurring or persistent swelling of the face and lips accompanied with facial paralysis or fissured tongue, MRS could be diagnosed [11].

No specific treatment has been identified for MRS, and the commonly used treatment methods including drug therapies and surgical treatments. In the present study, the patients were mainly treated with oral intake or intralesional injection of corticosteroids plus the administration of vitamins and acupuncture therapy. Complete recovery was found in 3 patients, remission was found in 28 patients, and the treatment failed in 1 patient. These findings suggest that these treatment methods are effective for patients with MRS; however, the clinicians and patients should pay attention to the recurrence of the disease. Bacci et al. [12,

13] have reported that intralesional injection of triamcinolone acetonide and 2% of lidocaine is the choice for treating cheilitis granulomatosa. The injection of 1.0 to 1.5 ml of triamcinolone acetonide (10 to 20 mg/ml) at each side of the involved lips could promote the regression of the inflammatory granuloma. In another study performed by Banks et al. [14], the combined use of minocycline and roxithromycin could effectively alleviate the edema. Helium-neon (He-Ne) laser therapy has also been demonstrated as an effective treatment method for patients with face and lips swelling less 4 years. Surgical treatments such as cheiloplasty could be performed for patients with giant lips which substantially affect the appearances; however, the recurrence of the disease and postoperative complications including sensory deprivation should be cautioned. Fortunately, Kruse demonstrated that cheiloplasty combined with intralesional injection of corticosteroids could effectively prevent the disease from recurring [15]. Treating early stage of facial paralysis with corticosteroids could achieve satisfactory effects, while facial nerve decompression should be performed for the treatment of facial paralysis or severe complications induced by facial paralysis. In the present study, decompression of the right facial nerve was performed for 1 patient, which resulted in satisfactory remission of facial paralysis. Previous studies have also demonstrated the efficacy of facial nerve decompression. In a study performed by Dutt et al. [16], a MRS patient with recurring intermittent facial paralysis for 13 years was treated with facial nerve decompression, and remission of the disease was found. However, recurrence of the disease was found in this patient, suggesting that this treatment method could alleviate the disease rather than cure it. In addition, systemic disorders could also play a role in the development of MRS [17].

In summary, MRS is a rare disease with relative high false-positive and false-negative rates. Genetic factors play a role in its development [18]. Most of the MRS are diagnosed in the department of neurology, dermatology, or ophthalmology and otorhinolaryngology [19, 20]. Clinicians in these departments should try to accumulate the experiences in treating related rare diseases. Facial nerve decompression was effective to prevent further episodes of facial palsy in MRS [21, 22]. Further studies are war-

ranted to investigate the immunological and neurological mechanisms involved in MRS to uncover more effective treatment methods [12, 23].

Disclosure of conflict of interest

None.

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