


Management Strategies of Melkersson-Rosenthal Syndrome: A Review

This article was published in the following Dove Press journal:
International Journal of General Medicine

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Abstract: Melkersson-Rosenthal syndrome is a rare disorder of unknown aetiology and characterized by the triad of oro-facial edema, facial nerve palsy, and furrowing of the tongue. Two or more of the above are essential for making a clinical diagnosis. The mainstay of treatment is corticosteroids. Intralesional triamcinolone acetonide may be used for the treatment of oro-facial edema. Another treatment option for oro-facial edema includes intralesional betamethasone, along with oral doxycycline. The review discusses the management strategies in Melkersson-Rosenthal syndrome.

Keywords: facial palsy, Bell's palsy, facial edema, lip edema, orofacial granulomatosis, recurrent facial palsy, fissured tongue, lingua plicata

Introduction

Melkersson-Rosenthal syndrome (MRS) is a clinical syndrome characterized by the triad of oro-facial edema, facial nerve palsy, and furrowing of the tongue. The syndrome was first described in 1928 by Ernst Gustaf Melkersson in a 35-year female with oro-facial edema and facial paralysis.¹ Associations of facial paralysis and fissured tongue (by Rosenthal) were described in 1931.^{2,3} The onset of symptoms is most commonly between 25 and 40 years (range 1–69 years), with a female preponderance (sex ratio of 2:1).^{4,5} MRS is rare in children, and only a handful of 30 cases have been described.^{6,7} Onset in children is common between 7 and 12 years of age, with the youngest child described at 22 months of age. The diagnosis is frequently delayed with the median time to the diagnosis being 4–9 years.⁷

Diagnostic Features

Melkersson-Rosenthal syndrome (MRS) is a clinical syndrome characterized by the triad of oro-facial edema, recurrent facial nerve palsy, and furrowing/fissuring of the tongue (also known as lingua plicata). Two or more of the above are essential for making a clinical diagnosis.⁸ Only one of the two clinical features is sufficient for diagnosis in the presence of histopathological evidence of granulomatous cheilitis in the biopsy of the eyelid or the lip. The term oligosymptomatic MRS is used when two clinical features are present, and monosymptomatic when only one symptom is present. The monosymptomatic cases are diagnosed when there is biopsy evidence of a non-necrotising, granulomatous cheilitis in patients with isolated facial or lip edema (Miescher MRS).⁹ In some cases, only lymphocytic inflammation around the blood vessels may be present, and frank granulomas may

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be absent. The histopathological findings may be missed if sampling is not done during the acute episodes.

The diagnosis is difficult in cases of isolated facial paralysis or isolated eyelid edema alone. Rarely, all the three features are present (20–75%).^{4,5} Isolated eyelid edema is a part of several diseases such as orbital malignancies, orbital pseudotumor, Grave's disease, and allergic disorders.¹⁰ Incomplete presentations often present to the dermatologist or the otorhinolaryngologist and may be missed if the suspicion is low, especially at a young age. However, the presence of recurrent facial nerve palsies in children should alert the treating physician to the presence of an underlying MRS. Facial palsy is usually the first clinical feature and precedes oro-facial edema by months to years. Facial paralysis may be unilateral or bilateral. Recurrent facial paralysis is seen in 10% of the cases.¹¹ Facial paralysis is seen in 30–90% of cases, and is associated with facial edema in 13–50% of cases.⁵ In a series by Tang et al, facial paralysis was bilateral in 40% of the cases.⁴ The duration of facial palsy increases as the disease progresses, with a tendency to become longer in duration.

Fissured tongue (lingua plicata) is defined as grooves on the dorsum of the tongue which are at least 2 mm deep and 15 mm long.¹² It is seen in 30–80% of cases of MRS.⁵ Fissuring may lead to secondary infections, hypertrophy, loss of papillae, loss of taste, and dysesthesia. Fissuring may be familial/hereditary. In a series of cases of MRS, 9% had fissuring since childhood, and 11% of the family members also had fissuring.⁴ Besides the three cardinal symptoms, migraine, headache, and dizziness were present in half of the patients.⁹ Other neurological symptoms which may be seen in MRS include tinnitus, deafness, facial paresthesias, difficulty in swallowing, hypogeusia, conjunctival congestion, aphthous ulcers, reduced or excessive facial sweating, excessive tears in the eye and visual disturbances. Other cranial nerves like trigeminal, olfactory, auditory, glossopharyngeal, and hypoglossal nerves can also be involved.¹³ Non-neurological symptoms include uveitis, diverticulitis, and ulcerative colitis. Recurrent episodes of MRS may lead to personality changes, anxiety, and depression.

Edema is painless, non-pitting and most commonly seen in the upper limbs, but may also be seen in lower lip, tongue, buccal area, eyelids, neck, gingiva, nose, upper arms, genitalia, and the larynx.^{4,5,7} Partial or non-resolution of edema may lead to fibrosis and may lead to permanent disfiguration of the face.

Etiology

The etiology of MRS is unclear. The etiopathogenesis of this rare pediatric disorder has been linked to HSV1 infections, hereditary granulomatous disorders, mycobacterial infections (tuberculosis, leprosy), chronic infections, Down's syndrome, psoriasis, thyroiditis, multiple sclerosis, keratitis, Wegener's granulomatous, diabetes mellitus, sarcoidosis, ulcerative colitis, and allergic disorders.^{5,7,14} Influenza respiratory infection may trigger a relapse of MRS. Gene mutations causing UNC-93B deficiency may predispose to HSV-1 infections.¹⁵ This deficiency selectively impairs immunity against HSV-1 but not against other organisms.¹⁶ Cases with a herpes-like lesion at the onset of facial edema have been described. Mutations in *FATP1* (fatty acid transport protein) have been described in one family.¹⁷ In another family, four generations of family members were affected due to an autosomal dominant transmission.¹⁸ Rare complications of MRS include sinusitis, candida infection, facial erythema, IgA nephropathy, vitiligo, thyroid hormonal abnormalities, and lacunar strokes.⁴ In the absence of clear-cut etiologies of MRS, terms MRS, cheilitis granulomatosa, granulomatous cheilitis, and monosymptomatic MRS are used interchangeably in different publications.¹⁹ Inflammatory bowel disease like Crohn's disease may present with oral manifestations such as lip swelling with fissures on lips, mucositis, gingivitis, glossitis, and cobblestone appearance of the oral mucosa.²⁰ There may occasionally be seen in MRS and confuse the clinical picture. Investigations are primarily directed to the exclusion of systemic etiologies (Box 1).

Treatment Corticosteroids

There is a significant role of abnormal immune function, immune deregulation, allergic tendencies in patients with MRS. So, short courses of immunosuppressants are often used in the treatment of MRS. There is no specific treatment for MRS. Traditionally, corticosteroids have been the mainstay of treatment.⁷ There are no randomized trials to suggest the corticosteroid type and duration that should be used. Therapy with corticosteroids leads to improvement in 50–80% of patients and reduced relapse frequency by 60–75%.⁷ Typically, oral corticosteroids are used for 1 week and tapered over 2 weeks. High-dose pulse methylprednisolone has been used in severe cases.

Treatment of Oro-Facial Edema

Intralesional triamcinolone acetonide (TA) (1–1.5 mL of 10–20 mg/mL solution) and lignocaine may be used in

Box 1 Investigations in Patients with Suspected Melkersson-Rosenthal Syndrome

<p>History and Examination</p> <p>Examination for enlarged nerves</p> <p>Otitis media</p> <p>Visual Acuity</p> <p>Hearing</p>
<p>Suggested Investigations</p> <p>Blood glucose, Complete blood counts, Erythrocyte sedimentation rate</p> <p>Liver and renal function tests</p> <p>CT scan of the head, MRI of the brain, Chest X-ray to rule out secondary conditions</p> <p>Angiotensin converting enzyme (ACE) levels</p> <p>Anti-nuclear Antibody (ANA) testing</p> <p>Antineutrophilic cytoplasmic antibody (ANCA)</p> <p>Thyroid function test</p> <p>Slit lamp for uveitis</p> <p>Brainstem evoked audiometry, visual evoked potentials</p> <p>Nerve conduction studies of facial nerve</p>
<p>Investigations in specialized scenarios</p> <p>Evaluation for tuberculosis</p> <p>Karyotyping for Down's syndrome</p> <p>HLA testing for Ulcerative colitis and Crohn's disease</p> <p>CI inhibitor deficiency test for hereditary angioneurotic edema</p> <p>Next generation sequencing</p>

local edema.²¹ In another study, a higher dose of intralesional TA of 40 mg/mL was used.²² TA was injected at four sides in each lip. Additional TA was injected in cheek and nasolabial folds. Three such weekly injections were given. The course was repeated after 6 months in case of persisting edema or recurrence. This treatment strategy leads to a significant decrease in the severity of edema as well as edema recurrences. The study was a retrospective study with 22 patients. Fourteen patients received only single injection and did not have any recurrence.²² The mean disease-free period after injection of TA was 28 months. All treated patients were disease-free after 2–4 weeks of injection with TA. Alternatively, intralesional betamethasone, along with oral doxycycline, may be used if TA is not available.²³ Eutectic lignocaine (prilox) may be used to reduce pain before intralesional injections. Intralesional TA is likely to be beneficial in cheilitis

granulomatosa without systemic disease. Doxycycline and minocycline have been postulated to inhibit of synthesis of protein kinase C.²³ Corticosteroid-antibiotic combinations with minocycline, and roxithromycin have also been used because of the possible anti-inflammatory effect in these two antibiotics.²⁴ We suggest oral corticosteroid if both facial paralysis and oro-facial edema are present, and intralesional injections if oro-facial edema alone is present or is refractory to oral corticosteroid.

Ancillary Treatment

Vitamins like thiamine, niacin, riboflavin, pyridoxine, ascorbic acid, and vitamin E have often been used along with corticosteroids. Other treatments tried with unproven benefits include benzoate-free diet, cinnamon-free diet, and acyclovir.^{25,26} Fumaric acid esters have an anti-proliferative effect on lymphocytes and macrophages. These medicines are used in the treatment of psoriasis and have shown some benefit in orofacial granulomatosis.²⁷

Other Immunosuppressants

In patients with other systemic involvement, immunosuppressants are also used. In possible cases of collagen vascular diseases, methotrexate,²⁸ thalidomide,²⁹ intravenous immunoglobulins, clofazimine,³⁰ dapsone,^{31,32} anti-TNF therapy (infliximab),³³ anti-histaminic drugs and hydroxychloroquine have been used in isolated cases.^{4,5,7} In a case report by Moll et al, a 69-year-old woman with MRS, type-2 diabetes and psoriasis was treated successfully by Adalimumab after 4 years of failed therapy.³⁴ It is hypothesized that tumour necrosis factor is responsible for granuloma formation and so anti-TNF like Adalimumab has been used in the treatment of psoriasis, Crohn's disease and sarcoidosis.³⁴ In another case, a 39-year woman with vulvar lump (histopathology showing tuberculoid-type granulomas) with a past history of MRS was successfully treated with Infliximab (chimeric monoclonal antibody).³³ In another case of 24-year woman with intralesional steroid refractory lip edema was treated successfully with Infliximab. In another series of 14 patients with oro-facial granulomatosis treated with Infliximab and Adalimumab, short-term response was seen in 70% of patients.³⁵ Adalimumab was effective in two patients who failed Infliximab. The authors suggest that patients with oral sulcus involvement, intestinal Crohn's disease and an elevated C-reactive protein are likely candidates of anti-YNF therapy.³⁵

Surgical Management

Surgical management may be done in recurrent facial palsies. The timing of surgery is uncertain. Total facial nerve decompression may be done by the middle cranial fossa approach. Standard mastoidectomy is done, and the facial nerve is decompressed from internal auditory meatus to geniculate ganglion. In one such study, none of the patients experienced a relapse of facial palsy compared to the patients who were treated medically.³⁶ Nearly 90% of patients who were operated recuperated to a near-normal status.³⁶ An alternate surgical approach like subtotal nerve decompression from stylomastoid foramen to geniculate ganglion can also be made.³⁷ This approach has a minor risk of conductive hearing loss.

Surgeries of lips may also be done for persistent lip edema. In one such case, based on Conway's technique, en-block removal of mucosa dorsal to vermilion was done.³⁸ Part of orbicularis muscle and grossly edematous tissue were also removed.³⁸ Helium laser ablation is an alternative procedure for cheiloplasty. Both these procedures may cause loss of sensation in the affected lip and do not affect disease recurrence.²⁴

Conclusion

Short duration oral corticosteroids are the mainstay in the treatment of MRS. Intralesional triamcinolone acetonide may be used in oro-facial edema. Refractory/recurrent MRS may need second-line immunosuppressants like methotrexate and thalidomide. Surgical decompression of the facial nerve may be considered in medically refractory recurrent facial nerve palsies. Cheiloplasty may be considered in cases of failure of triamcinolone acetonide.

Disclosure

The authors report no conflicts of interest in this work.

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