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Melkersson - Rosenthal Syndrome: A Literature Review of a Rare Syndrome with a Descriptive Case Report

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ABSTRACT

AIM

The aim of this article was to review the literature on the presentation and management of Melkersson Rosenthal Syndrome following the presentation of a 28-years-old patient who had been previously managed for recurrent bell's palsy for 5 years.

BACKGROUND

A computerized literature search using Medline, Science Direct and Google Scholar was conducted for published articles on manifestations, features and management of Melkersson Rosenthal syndrome. MeSH phrases like orofacial granulomatosis, Melkersson Rosenthal syndrome, Miescher's Cheilitis, Lingua Plicata, Cheilitis Granulomatosa, Recurrent Bell's palsy, Granulomatous Cheilitis, and MROS. Search parameter was set to select literatures under English language only. Adjunctive manual search was also conducted simultaneously to identify other published articles, considering similar parameters as used for Medline search.

RESULT

The review yielded 452 articles of which 168 articles were relevant to the discussion, less than 10 of these articles were from the African literature. We reviewed the literature for age, gender, incidence, prevalence, propounded aetiopathogenesis, risk factors, clinical manifestations, histopathological findings and treatment protocols.

CONCLUSION

The variable clinical manifestation of MRS may make early diagnosis difficult and even completely missed hence MRS should be considered as a probable diagnosis in patients with bell's palsy especially in recurrent and / or bilateral cases even in the absence of other clinical symptoms.

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CLINICAL RELEVANCE

This paper reviews the clinical manifestations of this rare lesion and its management especially in Sub- Saharan Africa where only a few of cases have been reported in documented literature. It also focused on the classes of drugs used in the medical management as only the first line of management of these drugs are available in low and middle income. We thus strongly believe that our manuscript represents a significant addition to the scientific literature as it pertains to occurrence and management of MRS in Sub-Saharan Africa.

KEYWORDS

Melkersson rosenthal syndrome; Orofacial granulomatosis; Miescher's cheilitis; Literature review

INTRODUCTION

Melkersson-Rosenthal Syndrome (MRS) is a rare, non-caseating, neuro-mucocutaneous, systemic granulomatous disease characterized by orofacial edema, relapsing facial nerve palsy, and lingua plicata (furrowed or fissured tongue) [1,2]. First described by Ernst Gustaf Melkersson in 1928 when he suggested a relationship between facial palsy and facial swelling [3]. Ekbom however that designated the condition a syndrome following Melkersson's early demise [4]. Curt Rosentahl in 1931 added furrowed/fissured tongue as the third association [3]. The description of several cases of isolated cheilitis granulomatosa by Miescher in 1945 prompted some authors to believe the disorder should be appropriately termed the Miescher Melkersson Rosenthal syndrome, although this classic triad defines the syndrome, it has only been documented to occur in about 8%-25% of all diagnosed cases of MRS and this triad need not exist for the diagnosis to be made [5,6]. The most frequent presentation of the disease is the monosymptomatic cheilitis granulomatosa (of Miescher) [7] occurring in about 42% of all MRS cases [2]. This orofacial swelling can manifest in any part of the face including the eyelids, cheeks, palate, gingiva, upper and lower lips. Facial palsy has been observed in about 20%-30% in MRS cases and it can be unilateral or bilateral (on both sides alternatingly, at the same time) [8,9]. The lingua plicata completes the triad and it is present in 30%-35% of MRS cases, however it is also found in 5% of the normal population hence, isolated fissured tongue cannot be diagnosed as monosymtomatic form of MRS [10,11] the triad symptoms/findings can be simultaneous or present at different times [12].

MRS is most frequently seen in the second or third decade of life with a female predilection [12], the etiology of MRS is still obscure with both genetic and acquired factors implicated [13]. Hornstein has suggested a polyetiologic cause [14]. A gene defect at chromosome 9 p11 has been related with MRS, with autosomal dominant inheritance pattern [15]. MRS sometimes manifest as a symptom of another condition such as Crohn's disease or Sarcoidosis for which they appear histologically similar [10], dietary and other allergens may also be involved. MRS is a clinical diagnosis hence histopathological finding are not necessary, however histopathology might help in differentiating it from Crohn's disease and sarcoidosis [16]. The characteristic histopathological features of MRS include granulomas with epithelioid cells, Langerhans type giant cells with multiple nuclei, perivascular mononuclear infiltration, non-caseating granulomas, lymphedema and fibrosis [16].

The treatment modality for MRS remains a challenge, anecdotal and should be based on the severity of the

clinical manifestations. It is very difficult to assess the efficacy of the therapeutic measures. Most regimens include corticosteroid therapy (topical, intralesional, or systemic) [17-19], antibiotics such as minocycline and doxycycline [19,20], non-corticosteroid regimens [21] and immunomodulators [22]. Although the response is usually temporary and sometimes ineffective with reported remission rate of 50% and 60%-75% recurrence in documented literature.1 MRS can remain undiagnosed for years especially when it presents with few clinical signs in its mono or oligosymptomatic forms [23]. This paper aims to review the literature on MRS with a descriptive case report of a patient who has been managed for years in the otorhinolaryngological unit for recurrent Bell's palsy.

CASE REPORT

A 28-years-old single female student, first presented at the general outpatient department of Aminu Kano teaching hospital with a presenting complaint of right facial weakness, deviation of angle of the mouth, inability to properly close the right eye and right ear hyperacusis of 2 weeks duration. An impression of Bell's palsy was made, patient was counseled and placed on systemic prednisolone (40 mg daily) for a week which was subsequently tailed down to 10 mg in 3 weeks. Artificial tears nocte for 2 weeks was also administered. Patient was reviewed after 2 weeks and gradual improvement in facial palsy observed. Patient presented 3 months after with recurrence in right facial palsy, hyperacusis and complained of excessive watery discharge from the right eye and conjunctivitis, patient also complained of tongue cracks and deep fissures. CNS examination reveals deviation of angle of mouth, lagophthalmos of the right eye but preserved sensory sensation.

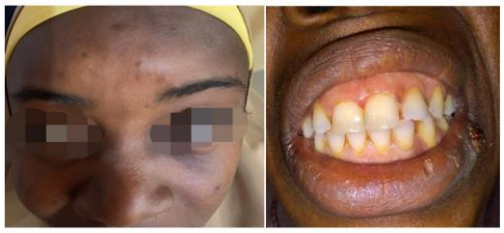

Figure 1: (A) shows flattened facial expression worse on the left (B) lower lip swelling with dry scales and a crusted nodule on the left commissure; gingival swelling is also seen.

Further systemic prednisolone was administered and patient advised to commence physiotherapy and patient monitored at subsequent follow ups. Sustained clinical improvement was observed at subsequent follow-ups.

Patient presented 5 years later with complains of left earache, left hyperacusis, lagophthalmos of the left eye and left facial weakness and otalgia of 7 weeks duration prior to presentation. She further complained of swelling of both upper and lower lips, persistent furrowing and fissuring of the tongue with ulcerations on the angle of the mouth. All these were confirmed on examination and a diagnosis of bell's palsy of the Left facial nerve made. Sickle cell disease, hypertension, diabetes mellitus and asthma were all subsequently ruled out and the retroviral status of patient confirmed to be negative. Following diagnosis, patient was again placed on systemic prednisone, neurobion and advised to restart physiotherapy on the left facial muscles. She was then referred to the oral diagnostic unit of dental maxillofacial department for management of the angular stomatitis and labial swellings. Patient presented in the dental unit with a complain of fissured tongue of 7 years, recurrent gingival swelling of 5 years, recurrent upper and lower lip swelling of 3 years and a relapsing left facial weakness. Additional complaints included left otalgia and hyperacusis, no altered taste sensation was observed. There were no contributory medical history, family history nor any associated disorders.

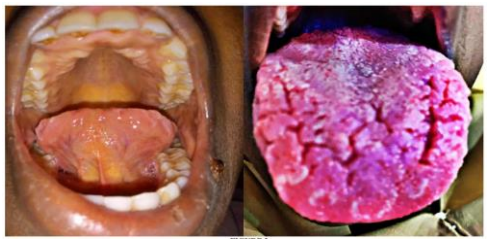

Figure 2: (A) shows polypoid gingival swelling, prominent rugae and high arch palate. (B) shows fissures and furrows of the tongue with macroglossia and circinate whitish deposits.

Examination revealed facial asymmetry with resolving weakness on the left side of the face evidenced by a flattened left side of the face and deviation of the mouth to the right side on opening. There was mild swelling of the lower lip which was firm and non-pitting, with loss of the normal creases of the lips and a crusted nodule on the left commissure. There was adequate mouth opening and generalized polypoid firm swelling of the gingiva, more prominent on the maxilla with very prominent palatal rugae and narrow palatal arch. Several fissures and furrows were present on the dorsum of the tongue with numerous small grooves and fissures running laterally from the middle third of the tongue with some extending to the lateral surfaces of the tongue: The tip of the tongue was however spared. There were also circular whitish rings close on the tip of the dorsal tongue and whitish coating on the posterior portion of the dorsal tongue: The tongue exhibited macroglossia. All the teeth are present in the mouth with no carious nor mobile teeth.

Full blood count, biochemical parameters and fasting blood sugar were within normal range. Based on the clinical findings, a diagnosis of Melkerson-Rosenthal syndrome was made. Treatment consisted of application of lip gloss to prevent further cracking of the exposed mucosa on the left lower lip, patient was told to continue the systemic prednisone prescribed by the ENT unit along with analgesics and physiotherapy. Patient was also referred for scaling and polishing and placed on warm mouth rinses. Following review of the patient after two weeks and 4 weeks respectively, no further treatment was deemed necessary and patient was placed on a three-month regular appointment.

DISCUSSION

Incidence and Prevalence

MRS is a rare orofacial granulomatous disease with equivocal etiology characterized by the classic triad of orofacial edema, recurrent facial nerve palsy and fissured/furrowed tongue. There is paucity of medical literature on its true incidence [24], however estimated reported incidence of 0.08% [6,13] or between 0.2-80 in 100,000 per year have been documented [12,25]. Gerensen et al. [23] hypothesized however, that the presumed rarity of MRS in literature is due to MRS being often undiagnosed when it presents with few clinical signs. In general, since its first description by Melkerson et al. in 1921, only about 300 cases of MRS have been reported with a chronic progressive course that span years and decades. MRS is most commonly found during the second to fourth decades of life [14,26], although it may affect any age group [27]. There are many published reports of MRS in children and pre-adolescents [20,28,29] and in adults over 40 years [26,30-32]: these are however rare [31]. Characteristically, at least one of its symptoms appear before the fifth decade [27]. The patient in our case study was in her third decade as at the time of presentation to the dental unit and also at the age of the first incidence of symptoms. Many documented studies report a slight predilection for females [25,27] while equal sex predilection, [14,18] or male predominance has also been reported [33]. The patient in our case study is of the female gender.

Review of the literature revealed that majority of MRS cases are Caucasoid and MRS has been reported more commonly in Europe than America [4,12]. However isolated cases have also been reported in Asia and middle Eastern countries [5,14,29]. Few case reports have also been documented in the African continent [19,34] more

less so in the sub-Saharan African [34] to the best of the author's knowledge, only one case report of Talabi et al. [35] has been documented in medical literature in Nigeria. No particular racial predisposition has however been reported in MRS [14,36].

Etiopathogenesis

The etiopathogenesis of MRS is equivocal at best with several hypotheses propounded to espouse its pathogenesis. The propounded hypotheses are mainly infectious, allergy and hypersensitivity to bacteria [13], hereditary or familial hypothesis and autoimmune dysregulation [2,4]; other less espoused theories include vasomotor disorder of the vasa vasorum [2]; neutrotrophic factors [37] and a micro-neurovascular etiology [1]. A genetic basis for pathogenesis has been supported by the aggregation of MRS within members of the same family [15] and a suggested de novo autosomal t(9;21) (p11;p11) translocation: this has however not be proven [1,37]. This is also corroborated by the fact that fissured tongue and unilateral facial nerve palsy (of Bell's) also have a genetic predisposition. Xu et al. [38] in their study described a gene mutation in fatty acid transport protein 1(FATP1) related to an MRS.

Despite allergies being mooted as a causative etiology, a specific allergen has not been identified neither is eosinophilia an observed histopathological feature of MRS [17], however allergies to food additives have been implicated. An increased or elevated eosinophilic and / or mast cell count has also not been described in documented literature to support an allergic etiology [17]. Vesicular eruptions with viral prodrome have been reported in a subset of MRS associations [17], Ang et al. [1] also described associations with previous odontogenic and adeno-tonsillar infection. Polymerase chain reaction for genomic sequences of HSV and other bacteria however yielded a negative result. Even though eradication of odontogenic infection presents a munificent effect on the oral mucosa, it does not resolve MRS spontaneously.

MRS has been observed in associated with a considerable number of autoimmune diseases namely Hashimoto's thyroidits, multiple sclerosis, psoriac arthritis and also with chronic granulomatous diseases such as Crohn's disease, tuberculosis and sarcoidosis [1]. These associations have reinforced its autoimmune etiology, this is also bolstered by the histologic presentation of non-caseating granulomas in its microscopic investigation. The role of anti-inflammatory medications (including anti-TNF-α) in its management also underlies the role of autoimmunity in its etiopathogenesis [39]. Expression of infiltrating mononuclear T helper lymphocytes which invariably produce interleukin 12 and interleukin 12 RANTES/MIP-1alpha have been observed in MRS with subsequent production of granulomas: HLA typing HLA-A2 or HLA-A11 have also been documented [39]. However, Hornstein in his neuro-mucocutaneous theory hypothesized that abnormal regulation of the autonomic nervous system induces overt permeability of facial cutaneous vessels with attendant hyper-stimulation of the perivascular tissue by infiltrating non-specific antigens [14].

CLINICAL MANIFESTATIONS

In spite of the fact that MRS has been reported as a triad of orofacial edema, cheilitis granulomatosa and lingual plicata: the full presentation of the triad has only been described in about 8%-30% [10,12,36] of MRS cases, the patient in our study presented with the full triad. Orofacial edema is the most common feature of MRS (and even though cheilitis granulomatosa is the most commonly prevalent form of this presentation, peri-orbital edema, buccal edema, peri-nasal edema and pan-facial edema have been reported) [1,10]. The upper lip is the most commonly prevalent area followed by the lower lip [1],

both upper and lower lips can also be simultaneously affected. The patient in our descriptive study had affectation of both upper and lower lips with accompanying dryness and scaling. The lip edema is usually asymmetric, non-specific, non-pitting, painless, firm and usually short-lived with irregular recurrence over several days and weeks. Chronic recurrence of the labial edema progresses slowly to a brawny consistency with varying forms of deformity; the initial edema might be persistent in about 25% of MRS cases [12]. Our patient elicited positive history of recurrent mild labial edema which are usually short lived but with increasing duration between relapses. Isolated cases of peri-orbital edema without labial edema have also been reported with MRS cases [32]. Due to its high incidence of orofacial edema in MRS (80%-100%) [23], clinicians have suggested facial edema should be a prerequisite for diagnosis of MRS [12]. Labial edema may be accompanied by dryness, scaling and ulceration as in our study. Ketabch et al. [14] hypothesized the alterations in lip architecture is due to the presence of lymphedema and non-caseating granuloma within the lamina propria. Asides facial edema, swelling of intra-oral structures including but not limited to the gingiva, palate, alveolar process, tongue (including macroglossia) has been reported in literature coupled with laryngeal and pharyngeal edema [23]. Polypoid swelling of the gingiva, prominent rugae and macroglossia were all observed in the case in our study, this could have however have been complicated by the poor oral hygiene observed in this patient. Nil evidence of laryngeal nor pharyngeal edema elicited Facial paralysis whose presentation clinically mimics Bell's palsy is found in present in 24%-90% of patients and it usually presents on the side of the orofacial swelling as with our patient [13]. The partial or complete facial palsy may be bilateral in 13%-50% of cases [13] but presents with alternating facial palsy of both sides amidst frequent recurrences. Recurrences become more prolonged and profound [14]: Facial nerve palsy of MRS can become permanent after several recurrent episodes [27]. The patient in this study presented with alternating (non-simultaneous) facial nerve palsy within the period of 5-years, there was nil episode of bilateral affectation. The right face was the first part affected by the palsy which incidentally is also the site of the asymmetric labial swelling. Leao et al. [40] attributed facial palsy to the pressure on the facial nerve as it courses through the facial canal or direct granulomatous infiltration of the facial nerve. Other neurological symptoms associated with the facial paralysis include alterations in taste, tinnitus, headaches and migraines. Involvement of other cranial nerves have also been reported with involvement of the trigeminal nerve [1] with accompanying painful presentation of MRS. Oculomotor nerve, olfactory and rarely the auditory, glossopharyngeal, vagus and hypoglossal nerves can also be affected [13]. Komurcu et al. [37] reported an associated hemifacial spasm with facial nerve palsy. Orofacial edema usually precedes facial palsy by several weeks or years and neurological symptoms are unrelated to whether patient have the full component of the MRS triad [12]. Occurrence of facial palsy before orofacial edema has also been documented [12,25], and in this study, the right facial nerve paralysis occurred 3 months prior to the onset of the labial swelling. The third component of the triad is fissured tongue or lingua plicata which is defined as the presence of at least 2 mm deep and 15 mm long grooves crossing through the dorsum and margins of the tongue [27]. It occurs in around 5% of the general population hence of lesser importance in the diagnosis of MRS [40]. It is however about 10 times more prevalent in MRS patients than the general population. It is found in about 33%-50% of MRS cases [5,10,37] and completes the triad: Isolated fissured tongue is not considered a spectrum of MRS as it occurs in a subset of the population and considered an anatomic variation. The patient in this study presented with multiple longitudinal and transverse fissures coursing through the

dorsum if the tongue to the lateral edges. Due to the variable presentation of this syndrome, patients may present with only the orofacial edema (cheilitis granulomatosa of Mischers) in the monosymptomatic form of MRS, or present with both facial edema and facial nerve palsy in its oligosymptomatic form. As the full triad is uncommon, mono-and oligo-symptomatic presentation may delay its diagnosis, this can also be complicated by the alternating presentations of its clinical manifestations. Delay in diagnosis of MRS cases have been reported in the literature with some lasting several decades [15] before being rightfully diagnosed by managing physicians. The patient in our study had been managed for about 5-years for a case of recurrent bell's palsy before the diagnosis of MRS in our dental facility. Some signs and symptoms defined as minor criteria are also part of Melkersson-Rosenthal syndrome [27]. The affection of other cranial nerves, migraine, salivary and lacrimal gland dysfunction and pupil motricity are the so-called minor criteria [36]. In addition, hyperhydrosis, hyperacusis, acroparesthesia, epyphora, hyperageusia and multiple ophthalmologic findings such as lagophthalmus, exposure keratitis, blepharocalasia, retrobulbar neuritis, retina vein anomaly and paralysis of medial rectus muscle have also been reported in MRS [36].

DIFFERENTIAL DIAGNOSIS AND ASSOCIATED LESIONS

MRS is a clinical diagnosis with the corollary of its symptoms whether in the mono-, oligo- or full triad guiding the clinician in its ultimate diagnosis. However, a litany of lengthy differential diagnosis should be excluded before a definitive diagnosis of MRS is arrived at. This list entails but not limited to lesions that present with swollen lips such as recurrent erysipelas, angioneurotic edema, lymphangioma, lymphoma, and herpes simplex labialis [1]. The most important in this group being angioedema which MRS must be definitively excluded from due to MRS chronic course and normal competent values. Lesions presenting with facial paralysis which MRS should also be excluded from include familial bell's palsy (which is also recurrent), motor neurone disease, Guillaine- Barre syndrome, Heerfordt's syndrome, myasthenia gravis, et al. [10,33,41] Association between MRS and chronic disorders such as Crohn's Diseases, sarcoidoisis, psoriasis, tuberculosis, leprosy and Hashimoto's thyroiditis have also been reported in documented literature[10,37,41] with its association with Crohn's disease and sarcoidosis being reported to be more than coupling coincidence especially as they all present histologically as non-caseating granulomas with overlapping clinical manifestations. Its increased incidence in patients with psoriasis has also been reported [42].

Steroids	Antibiotics	Antineoplastic Agents	Antimalarials	Anti-TNF-α	Calcineurin Inhibitors	NSAIDS [29,34]
Triamcinolone	Amoxicycline [34]	Methotrexate [5]	Chloroquine [5]	Adalimumab [22,37]	Tacrolimus [18]	
Betamethasone [19,34]	Doxycycline [34,37]	Thalidomide [18,37]	Hydroxychloroquine [5]	Infliximab [22, 37]		
Infliximab [22,37]	tetracycline [5, 37], minocycline [20]					
Tetracycline [5,37], minocycline [20]	Tetracycline [5,37], minocycline [20]					
	Dapsone [21,24], Sulfasalazine [5]					
	Dapsone [21,24] Sulfasalazine [5]					

Table 1: List of steroids, antibiotics, etc.

MANAGEMENT

Different modalities of treatment have been used in management of MRS primarily for the facial palsy and/or treatment for orofacial swelling with varying degrees of success and varying degrees of relapses. Different authors [18-22] have reported different medical therapies including monotherapy and combination therapy for the management of this syndrome with a plethora of medications ranging from steroids (intralesional and

systemic), antibiotics, analgesics, anti-TNF alpha, anti-neoplastic drugs, et al. Some authors have also recommended surgery as a modality for unremitting facial nerve palsy or incompletely resolved palsy [20] or in permanent fibrotic cases of the lip [14]. Treatment with steroids used singly or combined with alternative drugs is considered a mainstay of treatment [32] with different success rates in MRS; its main demerit being its deleterious effects when used for long term treatment. However, due to equivocal etiology and pathogenesis, the treatment of MRS is empirical and unsuccessful in some MRS cases; it is also propitiously self-limiting and resolves spontaneously in cases In resource limited centers like ours and other centers in Sub-Saharan Africa, steroids form the major mainstay of treatment due to accessibility and availability and it was reported to have been used in the case reports of Oudrhiri et al. [19] (in combination with doxycycline) and Brahams et al. [34]. The patient in our study was placed on systemic prednisone with a marked reduction in presenting symptoms with no relapse even after 3 months follow up. Other alternatives that have also been advocated but with equivocal results include radiotherapy, massage and electrical stimulation [27]. MRS is also not preventable as exact causes are unknown however avoidance of foods containing flavoring agents and/or preservatives have been advocated with treatment of any odontogenic focus of infection. Regular follow up and physical examinations are also advised. Complications include impaired vision, loss of taste sensations, permanent facial palsy, low self-esteem due to swelling on lips and face and in general an adversely affected quality of life.

CONCLUSION

Despite it being a rare syndrome, clinicians should have a high index of suspicion of MRS with patients presenting with recurrent facial nerve palsy with or without history of orofacial edema (not only cheilitis), and topical or systemic corticosteroids serve as the mainstay of treatment especially in resource limited centres with the options of other alternatives when lesion is unremitting or resistant to treatment.

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Nil

CONFLICTS OF INTEREST

None declared.

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