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Oro-facial granulomatosis. Response to elemental diet and provocation by food additives

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Summary

We report the case of an 8·5-year-old girl with oro-facial granulomatosis associated with clinical atopy, in whom relapse of her granulomatous disorder was shown to be related to exposure to specific food additives, viz. carmoisine, sunset yellow and monosodium glutamate. Treatment with a restricted diet resulted in considerable regression in the facial swelling which has been maintained for 6 months. A brief account of the histological features, both under light and electron microscopy, is given, together with a description of the use of nuclear magnetic resonance scanning in the assessment of this disease. The patient had no evidence to support a diagnosis of sarcoidosis or Crohn's disease.

Introduction

Oro-facial granulomatosis is characterized by the presence of chronic granulomatous lesions of unknown aetiology, involving, and apparently restricted to, the tissues of the face and mouth. It may be associated with a variety of neurological lesions, among which facial nerve palsy is the most common [1]. Notwithstanding earlier reports of similar patients, Melkersson [2] finally established the concurrence of facial oedema and recurrent facial nerve weakness, to which Rosenthal [3] added the description of fissuring of the tongue. Patients with cheilitis granulomatosa, described by Meischer [4] as chronic lip swelling due to granulomatous infiltration and lymphatic obstruction, were subsequently found to have histological features indistinguishable from patients with Melkersson–Rosenthal syndrome [5]. Oro-facial granulomatosis encompasses

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Fig. 1. Hypertrophy of the upper lip and swelling of the right cheek on presentation.

not only the Melkersson–Rosenthal syndrome and cheilitis granulomatosa, but also the oral manifestations of Crohn's disease [6, 7] and sarcoidosis [8,9]. The aetiology is uncertain: however, the increased prevalence of atopy and the implication of specific food intolerance [10,11] suggests a possible allergic basis for this syndrome in some patients.

Case report

History

An 8·5-year-old Irish girl was referred in May 1984 with a 4-year history of chronic, intermittently more severe swelling of the upper lip and gum associated with fissuring, cracking and bleeding, which began following an episode of severe stomatitis and ulceration of the oral mucosa. This seemed to be worse towards the evening and was aggravated by infections, emotional stress and antibiotic therapy, but apparently not by food.

In 1977, following the second of two episodes of upper respiratory tract infection, she experienced a febrile convulsion with right-sided facial weakness and twitching of the left arm and leg. Examination revealed pharyngitis, cervical lymphadenopathy and

a generalized rash, although routine investigations (including chest and skull radiographs and examination of the cerebrospinal fluid) were normal. Despite adequate anticonvulsant therapy she experienced recurrent epileptiform seizures, although her electroencephalogram (EEG) was normal. As phenobarbitone made the patient irritable, her therapy was altered to sodium valproate which was continued until 7 years of age. There was also a history of infantile eczema and pertussis associated with lobar pneumonia. She had an adeno-tonsillectomy in 1979 for severe mechanical obstruction of the nasopharynx. More recently she had developed conjunctivitis on contact with cat and horse dander. During 1981 investigations revealed that serum immunoglobulins were normal except for a significantly elevated IgE (138 IU/ml).

Investigations

Allergen specific IgE showed moderate reactivity with grass pollen and cat dander, but very high reactivity with house dust mite. Complement studies including C_1 esterase inhibitor were normal, but she had a positive smooth muscle antibody immunofluorescent titre at 1:20. She was advised to avoid foods containing colouring agents, although a completely colouring-free diet could not be observed. The swelling of the lip continued to wax and wane, accompanied by an episode of right facial asymmetry, which recovered spontaneously.

Family history

There was a strong family history of atopy: a sister (10-years-old) and brother (7-years-old) had asthma and eczema; her paternal grandfather and a maternal uncle were asthmatic. Her youngest brother had severe eczema associated with milk allergy. Her father had hay fever and both he and her youngest brother had experienced febrile convulsions. No other member of the family had similar symptoms and signs to our patient.

Further investigation

She was referred for further investigation in May 1984. Examination confirmed her swollen upper lip, a spongy and hypertrophied gum and mild oedema of the right cheek (Fig. 1); cervical lymphadenopathy was present, but there were no other physical signs. The following investigations were performed: full blood count, white cell count and differential, platelets and ESR normal; film revealed anisocytosis; prothrombin time, partial thromboplastin time, thrombin clotting time normal; urea and electrolytes, liver function tests, serum calcium, phosphate and urate normal; autoantibody screen, including latex, RAHA and smooth muscle antibody tests were negative. Serum immunoglobulins: IgG 11·2 g/l (NR 4·7–14·4), IgA 1·5 g/l (NR 0·3–2·1), IgM 1·4 g/l (NR 0·4–2·3); total IgE 125 (IU/l); serum protein electrophoresis normal. Total haemolytic complement 100% (NR 60–140), C4 component 82% (NR 60–140), C3 component 140% (NR 70–125); C_1 esterase inhibitor 100% (NR 50–150); C3d 105% (NR 40–130); opsonin index 3·35 (normal greater than 2·8). Toxoplasma dye test titre was not significant at 1:16; swab of buccal mucosal ulcer was negative for herpes simplex. Throat swab produced significant growth of Lancefield group G haemolytic streptococci which subsequently disappeared. Mantoux 1:1000 and candida intradermal skin-prick tests were negative at 48 h; positive skin-prick tests to house dust, feathers, pollens, dog, cat and horse hair were elicited at 20 min, but only the horse hair



Fig. 2. NMR scan of head and neck on presentation showing normal cerebral hemispheres, brainstem and cerebellum in the presence of gross swelling of the upper lip.

reaction persisted to 2 hr. Kveim test with intracutaneous injection of 0·1 ml antigen from spleen K12 (lot 1) yielded no papule at 4 weeks. Serum angiotensin-1-converting enzyme (ACE) was not elevated on two occasions, viz. 43 (19.6.84) and 23 (2.7.84) nmol/ml/min respectively (NR 16–52) nmol/ml/min. Histology of a lip biopsy performed at this time revealed the presence of granuloma formation with surrounding lymphocytic infiltration. There were no specific ultrastructural features within the epithelioid cells, which showed changes typical of such cells within the sarcoid



Fig. 3. Regression of swelling of upper lip and cheek following introduction of a total elemental diet.

granuloma. A nuclear magnetic resonance (NMR) scan of the head and neck demonstrated profound swelling of the upper lip, with normal lower lip, cerebral hemispheres, brainstem and cerebellum (Fig. 2).

Management

A diagnosis of oro-facial granulomatosis was made. Despite strict adherence to a diet which excluded food colouring, monosodium glutamate, benzoate preservatives and salicylates, the lips became progressively more swollen with involvement of the lower lip for the first time. Despite this a double-blind challenge 2 weeks later produced a rapidly developing and severe reaction to carmoisine and sunset yellow, with profound swelling of the lips and cheeks and buccal mucosal ulceration. A less marked reaction was observed with monosodium glutamate. Whilst additives were clearly a cause of exacerbation it was likely that other foods were involved and therefore a total elemental diet initially with Vivonex alone and later with soy milk led to a gradual improvement. New foods were re-introduced into her diet one by one at 4-day intervals. She has, thus far, tolerated all meats, fish, wheat, oats, several vegetables, tea, coffee and apples. However, sausages produced a reaction, perhaps because of their monosodium glutamate content.

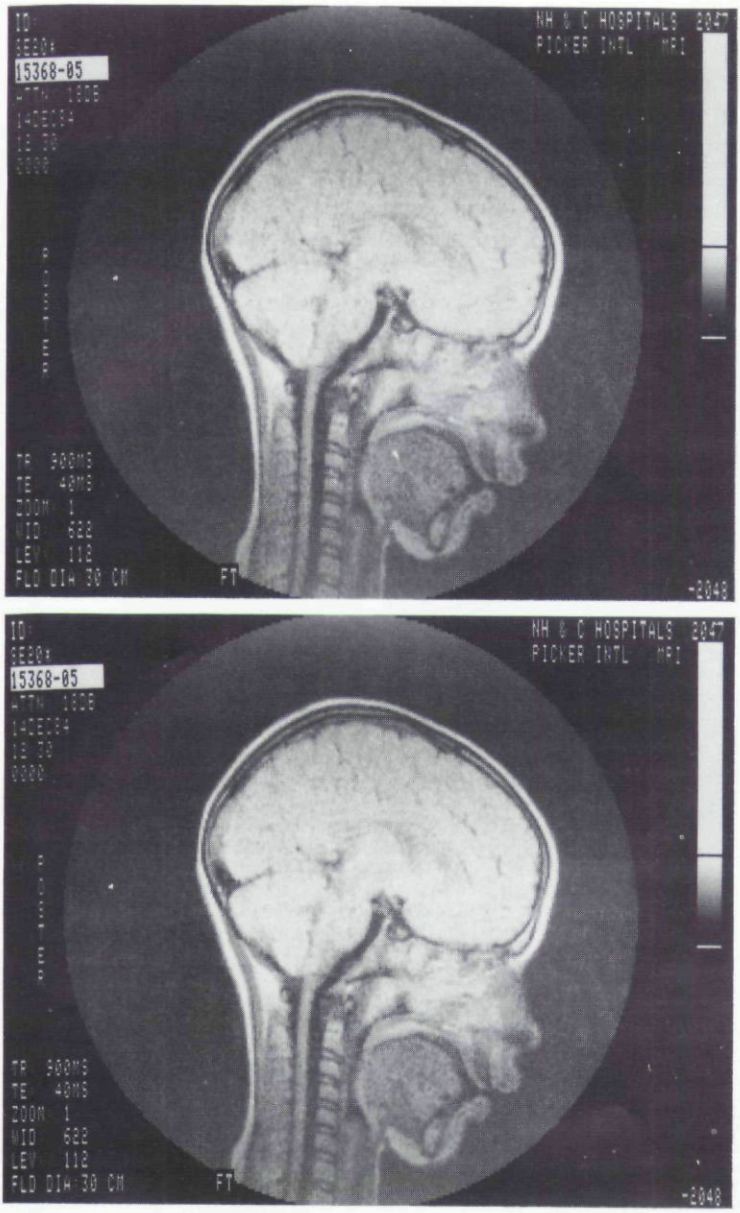


Fig. 4. NMR scan confirming regression of upper lip swelling.

In October 1984 she experienced another epileptiform seizure and on this occasion the EEG was unequivocally abnormal with generalised epileptic discharges. She therefore recommenced sodium valproate therapy. On review 6 months later the swelling had subsided considerably (Fig. 3) and a second NMR scan confirmed the reduction in the upper lip size (Fig. 4).

Discussion

The clinical hallmark of oro-facial granulomatosis is swelling of the lips and face,

varying from diffuse hypertrophy of the lower face to localized involvement of lip or cheek [1,12]. The lip is the most common site of involvement, often intermittent at first, although eventually becoming chronic in most cases, and fluctuation in severity may be related to local infection [1,13,14]. Painful vertical fissures, angular cheilitis, and oral mucosal abnormalities (such as extensive thickening, oedema, discrete tags or ulceration) also occur. Patchy gingival erythema and hyperplasia may be found [12]. Fissuring of the tongue is a relatively common finding in the general population [1], and may be of little significance [1,12]. Facial nerve palsy is the most common associated neurological lesion [12,14], but other cranial nerve palsies, transient encephalomyelitis, Horner's syndrome and psychosis [1] have also been described. There are reports of diminished intellect and consistently abnormal EEGs after onset of oro-facial granulomatosis [1,13].

The most frequent histological feature is oedema of the superficial corium with lymphatic dilatation and a predominantly lymphocytic (either perilymphatic or diffuse) inflammatory infiltrate [12]. Non-caseating granulomas (rarely containing small areas of central necrosis) are found mainly in the lamina propria, but also occur in more deeply situated tissues, including skeletal muscle and salivary glands; they are mostly small and relatively poorly-formed, consisting of epithelioid histiocytes, lymphocytes and often, but not always, multinucleate giant cells [12,14]. (A few contain birefringent intracellular foreign material of undetermined significance).

These granulomas are distinguishable from those occurring in gastrointestinal Crohn's disease or sarcoidosis; oral lesions are now well recognized in the former, either preceding [6] or concurrent with gastrointestinal involvement [15]. Some authors have reported an incidence between 10–37% of Crohn's disease in patients with oro-facial granulomatosis [7,12], while other series have found no association [14]. Our patient had no gastrointestinal symptoms, and neither haematological nor biochemical evidence of malabsorption; no extra-intestinal lesions of Crohn's disease were present and this would seem an unlikely diagnosis. Sarcoidosis may rarely present with clinical features resembling oro-facial granulomatosis, including similarly localized oedema and granulomatous infiltration. (Mucosal nodules, regional lymphadenopathy [10] and salivary gland infiltration may occur.) However, in our patient, serum ACE and chest radiographs were consistently normal, and intracutaneous injection of Kveim antigen failed to produce a papule at 4 weeks, so that a diagnosis of sarcoidosis was improbable. Infective granulomatous disorders, e.g., tuberculosis and leprosy, seemed improbable in the face of a normal chest radiograph, negative Mantoux reaction (1 : 100PPD) and lack of travel to endemic areas for leprosy.

Several mechanisms have been proposed for oro-facial granulomatosis, including allergic reaction to a variety of non-specific agents [1], hypersensitivity to bacterial products [17] and focal dental infections [14]. More extensive studies [12] have not confirmed isolated reports [3,18] of a genetic component. The patient reported here had a strong family history and substantial clinical evidence of atopy, findings entirely consistent with current observations of the increased prevalence of clinical atopy in this disorder [10]. Patton *et al.* [11] have recently demonstrated that specific food intolerance is an aetiological factor in oro-facial granulomatosis; in their series of eighty patients fourteen (17·5%) were intolerant to specific foods or flavouring, and thirteen of these were clinically atopic. Constituents likely to provoke granuloma formation include cinnamaldehyde (and probably cinnamon), carbone, piperitone and cocoa [11]. Double-blind challenge in our patient produced marked reactions to

carmoisine, sunset yellow and monosodium glutamate, but overall regression of her symptoms was only achieved with a total elemental diet. These food constituents have not been previously identified as major provoking factors in oro-facial granulomatosis.

Results of treatment of this condition, whether with systemic or intralesional steroids, or azathioprine, salazopyrine, topical cromoglycate or surgical reduction, have so far remained disappointing [11]; thus the initial response to an elemental diet in this patient is encouraging. Food intolerance may represent a primary response to an allergen, or exacerbation of pre-existing disease. Elevated immunoglobulin levels (i.e., IgE, IgG) and positive skin tests are not universal among patients with oro-facial granulomatosis; the latter does not seem to be a Type 1 reaction and it may be that the increased prevalence of atopy initiates an abnormal cell-mediated response [11].

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