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ORIGINAL ARTICLE

Characteristics of patients with orofacial granulomatosis

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OBJECTIVES: Orofacial granulomatosis has mostly been described in reports of very small numbers of cases. Few large case groups have been described. The aim of this study was to describe the demographics, symptoms, clinical features and laboratory findings in a large cohort of cases.

SUBJECTS AND METHODS: Clinical and laboratory data for 119 cases of orofacial granulomatosis who attended oral medicine clinics in Dublin, Ireland, were examined for demographic characteristics at the time of first presentation. The male/female ratio was approximately 1:1, with a median age (and range) of 28 (5–84) years.

RESULTS: Symptoms had been present for a median duration of 12 weeks. A food association was suspected by 30% of patients. The predominant complaint was lip swelling (77%) with only 15% reporting facial swelling, while 8% complained of both. Almost all patients had clinical evidence of lip or facial swelling (95%). Other common extra-oral manifestations were lip fissuring (30%), angular cheilitis (28%) and perioral erythema (28%). Common intra-oral manifestations were cobblestoning of the buccal mucosa (63%), ulcers (36%), granulomatous gingivitis (33%), mucosal tags (29%) and fissured tongue (17%). Over half of the biopsies (56%) performed were reported as typical of orofacial granulomatosis.

CONCLUSION: This is one of the largest cohorts of orofacial granulomatosis patients to have been described in detail.

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Keywords: orofacial granulomatosis; granulomatous cheilitis; Miescher's cheilitis; Melkersson--Rosenthal syndrome; oral Crohn's disease

Introduction

Orofacial granulomatosis (OFG) is a term devised to cover a variety of granulomatous, oedematous conditions of the lips and face (Wiesenfeld *et al*, 1985). Orofacial granulomatosis was described as granulomatous cheilitis by Miescher (1945) and as part of the Melkersson–Rosenthal syndrome, a triad of swollen lip, fissured tongue and facial palsy (Melkersson, 1928). There are several recent reviews of OFG (Leão *et al*, 2004; Tilakaratne *et al*, 2008; Grave *et al*, 2009).

In reviewing the literature, we were very aware of the varying qualifications given to the term OFG. Some use the term to denote all conditions with evidence of granulomatous inflammation of the orofacial region regardless of cause and thus include Crohn's disease (Dudeney and Todd, 1969; Issa, 1971), while others exclude cases with gut Crohn's disease. This, however, does not exclude the possibility that all cases of OFG represent Crohn's disease restricted to the face and mouth. It is not possible on clinical or histological appearances to distinguish the lip lesions found in OFG and oral Crohn's disease (Tyldesley, 1979; Pittock *et al*, 2001) or Melkersson–Rosenthal syndrome (Hornstein, 1973; Wiesenfeld *et al*, 1985).

Early reports that all OFG cases progress to Crohn's (Tyldesley, 1979) are not now accepted (Greene and Rodgers, 1989). Several recent reports (Sanderson *et al*, 2005; Campbell *et al*, 2011) have postulated that some cases of OFG may be an inflammatory bowel disease, distinct from oral Crohn's disease; the latter report has even suggested the possibility of three distinct groups: classical oral Crohn's, the new inflammatory bowel-associated OFG and a form of OFG with no bowel involvement.

Other granulomatous diseases suggested as causative of OFG include mycobacterial infection (Apaydin *et al*, 2000, 2004) and sarcoidosis (van Maarsseveen *et al*, 1982; Bourgeois-Droin *et al*, 1993), although the evidence for both is tenuous.

A suggested cause of OFG in the absence of systemic granulomatous disease ('idiopathic' OFG) is allergy (Patton *et al*, 1985; Wiesenfeld *et al*, 1985; Haworth *et al*, 1986; Sweatman *et al*, 1986; Pachor *et al*, 1989; Oliver *et al*, 1991; Reed *et al*, 1993; McKenna *et al*, 1994; Gibson *et al*, 1995; Levy *et al*, 1996; Armstrong *et al*, 1997; Wray *et al*, 2000; Taibjee *et al*, 2004; White

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et al, 2006; Endo and Rees, 2007). A number of dental hygiene products and food-associated allergens have been implicated in the aetiology of OFG; these include toothpastes (and other dental hygiene products), cocoa/chocolate, cinnamon compounds, carvone, piperiton, carmoisine (E122), sunset yellow (E110), monosodium glutamate (E621), benzoates (E210-219) and tartrazine (E102) (Patton *et al*, 1985; Ferguson and MacFadyen, 1986; Haworth *et al*, 1986; Sweatman *et al*, 1986; Oliver *et al*, 1991; McKenna *et al*, 1994; Armstrong *et al*, 1997; Wray *et al*, 2000; Taibjee *et al*, 2004; Fitzpatrick *et al*, 2010). In some cases, subsequent elimination diets have had some success in reducing clinical features (Patton *et al*, 1985; Haworth *et al*, 1986; Sainsbury *et al*, 1987; Armstrong *et al*, 1997; Wray *et al*, 2000; White *et al*, 2006; Endo and Rees, 2007). Allergy to various dental restorative materials (Pryce and King, 1990; Guttman-Yasky *et al*, 2003; Lazarov *et al*, 2003) has also been suggested.

The true prevalence of OFG is unknown, as there are no reliable epidemiological data, but a figure of 0.8% (800/100 000 persons) has been suggested (Mahler and Kiesewetter, 1996). It has been suggested that OFG is more prevalent in 'Celtic' populations (Challacombe, 1997). Studies with 20 or more subjects would tend to suggest that OFG is a condition principally of children and young adults (Ferguson and MacFadyen, 1986; Hornstein *et al*, 1987; Zimmer *et al*, 1992; Sanderson *et al*, 2005; Al Johani *et al*, 2010).

The principal oral and facial features of OFG are lip swelling (which may affect one or both lips, on one or both sides, with or without fissuring), angular cheilitis, swelling of the cheek (both extra and intra orally), full-thickness gingivitis, fissured tongue, mucosal tags, linear oral ulceration and a cobblestone or 'basket of eggs' appearance of the buccal mucous membrane (Wiesenfeld *et al*, 1985).

Biopsy of affected tissues typically shows non-caseating granulomas, with or without multi-nucleate giant cells, and lymphangiectasia and perivascular lymphocytic infiltration (Wiesenfeld *et al*, 1985). However, a non-specific inflammatory infiltrate may be the only histopathological finding (Ferguson and MacFadyen, 1986; Greene and Rodgers, 1989; Zimmer *et al*, 1992).

We have identified 15 reports of six or more cases of OFG and/or Melkersson–Rosenthal syndrome and/or oral Crohn's disease within the last 30 years (Hornstein, 1973; Tyldesley, 1979; Worsaae *et al*, 1982; Wiesenfeld *et al*, 1985; Ferguson and MacFadyen, 1986; Allen *et al*, 1990; Zimmer *et al*, 1992; van der Waal *et al*, 2002; Handa *et al*, 2003; Mignogna *et al*, 2003; Sciubba and Said-Al-Naief, 2003; El-Hakim and Chauvin, 2004; Sanderson *et al*, 2005; Al Johani *et al*, 2010; Campbell *et al*, 2011), ignoring other, partial reports of some of these series. We are unsure to what extent the series of Wiesenfeld *et al* (1985) and Ferguson and MacFadyen (1986) overlap and to what extent the cases reported by Sanderson *et al* (2005) are included in the larger series reported by Campbell *et al* (2011).

As OFG has been poorly defined and described in many of the earlier studies, the aim of the present study was to describe the demographics, clinical features and laboratory findings in a large cohort of persons with OFG. We have chosen to use the term OFG in the sense of any non-caseating granulomatous enlargement of the lip, face or oral tissues, with or without other local features, unless confirmed as Crohn's disease.

Patients and methods

OFG cases that had been seen in the oral medicine clinics in the Dublin Dental University Hospital and the City of Dublin Skin and Cancer Hospital (Hume Street Hospital) for the 21 year period from 1988 to 2008 were selected for study. Any patients with clinical features suggestive of OFG were included, provided they were not subsequently diagnosed with Crohn's disease. Patients under active treatment and those whose records were archived were selected. Many of the patients had attended the oral medicine clinics in both hospitals and had also attended the dermatology clinics in Hume Street Hospital. As this latter hospital is now closed, there were some difficulties in obtaining full records for some patients. In addition, some records from the Dublin Dental University Hospital, predating the introduction of an electronic patient index, were not retrievable. Records were retrieved via histopathological records and patch test registers and from a database that had been compiled some years earlier. In all, 129 relatively complete records were retrieved. Examination of the records showed that ten patients were diagnosed with Crohn's disease as part of the initial investigation or subsequently. This left 119 OFG cases, according to our stated criteria.

Patient records were examined for details of history, examination and those laboratory investigations that were felt at the time of examination to be relevant in the diagnosis of OFG. This was a retrospective study, and data were retrieved from records only; no patients were re-interviewed.

Statistical analysis of the data was carried out on male/female differences, using the chi-squared test, Fisher's exact test or the Mann–Whitney U test, as appropriate. The results are reported only where statistically significant ($P < 0.05$).

Results

Demographic details

Fifty-seven (48%) of the cases were men and 62 were women. The median age (and range) at presentation was 28 years (5–84 years). The median age (and range) for men was 23 years (5–80 years) and for women 30 years (6–84 years). This difference was statistically significant; however, when age was corrected to age at onset by subtracting duration, this significant difference disappeared. Details of age and sex are given in Figure 1. All patients were Caucasian. Almost half of cases had been referred by general dental practitioners and almost half of the remainder by dermatologists. Occupation was recorded in 81 cases. Forty-three of these (53%) were

schoolchildren or college students. The remainder had a variety of manual, clerical and professional occupations.

Patient complaints and histories

The principal presenting complaints were recorded in all cases. Ninety-two patients (77%) complained of lip swelling, and 18 (15%) complained of facial swelling. Ten patients (8%) had a swelling of both lip and face. Twelve patients (10%) complained of oral ulceration. Details of the principal presenting complaints are shown in Table 1, and details of the principal features elicited in patient histories are shown in Table 2. Duration of symptoms at first visit was recorded in 116 cases (56 men and 60 women). The median duration (and range) was 12 weeks (1–360 weeks); men 12 weeks (1–144 weeks); women 16 weeks (1–360 weeks), see Figure 2.

Symptom histories

All cases gave a positive history of swelling; 75 (63%) of these had lower lip swelling, 75 (63%) upper lip, 42 (35%) both lips, two (2%) lip unspecified, 29 (24%) face, four (3%) buccal mucous membrane, two (2%) floor of mouth and one (1%) palate. Twenty-three cases (19%) had had swelling of both face and lips.

Details of ulceration were recorded in 112 cases; 42 (38%) reported mouth ulcers; details of angular cheilitis were recorded in 102 cases; and 34 (33%) gave a positive history.

Table 1 Principal presenting complaint of 119 orofacial granulomatosis cases

Principal presenting complaint	*Males*	*Females*	*Both*
Lip swelling	44	48	92
Facial swelling	11	7	18
Both lip and facial swelling	7	3	10
Angular cheilitis	1	0	1
Lip fissuring	0	1	1
Intra-oral buccal swelling	1	1	2
Floor of mouth swelling	1	0	1
Oral ulceration	7	5	12
Perioral erythema	6	10	16
Gingival symptoms	0	3	3

Table 2 Principal anamnestic features of 119 orofacial granulomatosis cases

Anamnestic feature	*Number of records*	*Number (%) with feature*	*Males (%)*	*Females (%)*
Lip and/or facial swelling	119	114 (96)	55 (96)	59 (95)
Lip swelling	119	110 (92)	55 (90)	55 (93)
Upper		75 (63)	43 (70)	32 (55)
Lower		75 (63)	31 (51)	44 (76)
Both		42 (35)	19 (31)	23 (40)
Unspecified		2 (2)	0	2 (4)
Facial swelling	119	29 (24)	15 (27)	14 (24)
Bowel symptoms	116	21 (18)	8 (15)	13 (21)
Angular cheilitis	102	34 (33)	17 (37)	17 (30)
Facial palsy	112	9 (8)	3 (6)	6 (10)
Oral ulcers	112	42 (38)	20 (36)	22 (39)

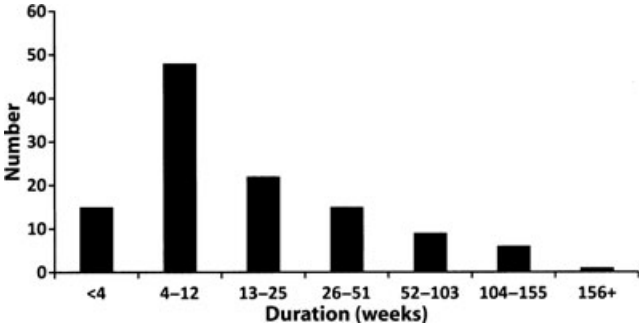

Figure 1 Age and sex distribution of 119 orofacial granulomatosis cases

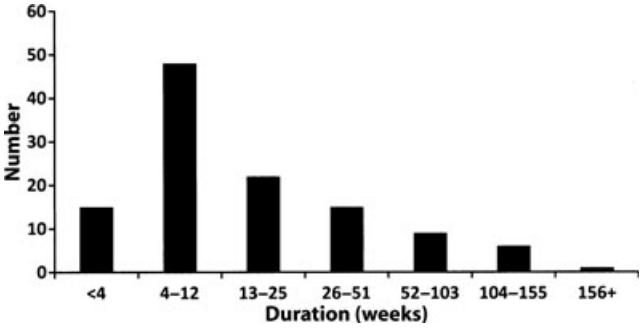

Figure 2 Duration of symptoms in 119 orofacial granulomatosis cases prior to first attendance

Records of facial palsy status existed for 111 cases; nine (8%) gave histories of previous or current facial palsy. In five patients, the facial palsy had occurred many years before: 9, 10, 12, 13 and 30 years, respectively.

Details of possible food associations were recorded in 111 cases. Thirty-three patients (30%) felt that there was a food association with their condition. The principal foods implicated were chocolate (13, 39%), carbonated drinks (7, 21%) and beer (5, 15%). Two patients claimed toothpaste as a trigger.

Relevant medical histories

Details of histories of atopy and allergy were each recorded in 80 cases. The most common atopic conditions were asthma (16 cases), hay fever/rhinitis (14 cases) and eczema (14 cases).The most common allergies were penicillin (five cases), house dust (four cases) and cats (four cases).

Bowel histories were recorded in 116 cases. Twenty-one patients had bowel symptoms; eight of these had minor symptoms such as flatulence, bloating or mild cramps.

Clinical findings

The clinical findings are summarized in Table 3. Details of face and lip swelling were available for all cases. Some degree of lip or facial swelling was recorded in 113 cases (95%). Six (5%) had neither lip nor facial extra-oral swelling. Swelling could affect one or both lips plus or

Table 3 Clinical features of 119 orofacial granulomatosis cases

Clinical feature	*Number of records*	*Number (%) with feature*	*Males (%)*	*Females (%)*
Lip swelling	112	102 (91)	52 (93)	50 (89)
Upper		69 (61)	30 (54)	39 (70)
Lower		46 (41)	22 (39)	24 (43)
Both	103	36 (32)	22 (39)	14 (25)
Unspecified		2 (2)	1 (2)	1 (2)
Bilateral		49 (48)	23 (47)	26 (48)
Facial swelling	119	36 (30)	18 (32)	18 (29)
Bilateral	35	5 (14)	3 (17)	2 (12)
Lip fissuring	109	33 (30)	21 (42)	12 (20)
Angular cheilitis	107	30 (28)	17 (35)	13 (22)
Cobblestoning	117	74 (63)	47 (84)	27 (44)
Mucosal tags	105	30 (29)	16 (33)	14 (25)
Tongue fissuring	108	18 (17)	8 (16)	10 (17)
Oral ulcers	109	39 (36)	20 (40)	19 (32)
Pyostomatitis vegetans	103	5 (5)	2 (4)	3 (5)
Granulomatous gingivitis	106	35 (33)	13 (28)	22 (37)
Perioral erythema	58	16 (28)	6 (24)	10 (30)

minus facial swelling, see Table 3. One hundred and two cases (86%), 52 women and 50 men, had lip swelling. Of the cases with lip swelling, 36 (35%) had swelling of both lips. 33 (32%) had upper lip swelling only, 10 (10%) had lower lip swelling only and two (2%) had unspecified lip swelling. The presence or absence of bilateral lip swelling was recorded in 103 cases; 49 (48%) had bilateral lip swelling.

Details of facial swelling were recorded in all cases. Thirty-six cases (30%) had facial swelling. The presence or absence of bilateral facial swelling was recorded in 35 cases; five (14%) had bilateral facial swelling. The presence or absence of lip fissuring and angular cheilitis was recorded in 109 and 107 cases, respectively; 33 (30%) had lip fissuring and 30 (28%) had angular cheilitis. Lip fissuring was statistically significantly more likely to be found in men.

Intraorally, the presence or absence of a cobblestone appearance of the buccal mucous membranes was recorded in 117 cases; 74 (63%) had cobblestones. Forty-seven of 56 men (84%) had cobblestoning *vs* 28 of 62 women (45%); this difference was statistically significant. The presence or absence of mucosal tags was recorded in 105 cases; 30 (29%) had tags.

The presence or absence of tongue fissuring was recorded in 108 cases; 18 (17%) had fissures. The presence or absence of oral ulcers was recorded in 109 cases, with 39 (36%) having oral ulcers. The presence or absence of a clinical appearance suggestive of pyostomatitis vegetans was recorded in 103 cases; five (5%) had this typical appearance. The presence or absence of typical gingival involvement ('full-thickness' granular gingivitis involving the attached gingivae) was recorded in 106 cases, with 35 (33%) having this finding. The presence or absence of perioral erythema was recorded in 58 cases, and it was present in 16 patients (28%).

Those patients with significant bowel symptoms ($n = 14$) were referred for gastroenterology opinions; eight of these underwent endoscopy, with negative results.

Histopathology

Biopsy reports were available for 85 patients (71%). Forty-eight biopsies (56%) were reported as definite OFG with a further seven (8%) reported as suspicious of OFG. In 58 cases (68%), non-caseating granulomas were seen; 21 cases (25%) showed oedematous changes, and eight (9%) were reported as showing lymphangiectasia. Forty cases (47%) showed chronic inflammatory cell infiltration.

Laboratory investigations

Analysis of various haematological indices and immunological tests showed few consistent significant patterns of variation from normal values (Table 4). Six of 102 cases had low haemoglobin; all were women. Twenty-five of seventy cases (36%) had low lymphocyte counts; there was no marked sex difference. Fifteen of 64 cases (23%) had low ferritin levels; this was more marked in women. Only four of these cases had the patterns of haematinic changes typically associated with iron deficiency. Two of the three cases with red cell folate deficiency also did not show changes on their full blood counts. Eleven of 61 cases (18%) had elevated levels of alkaline phosphatase; the majority were men. One case of 80 tested had elevated serum angiotensin-converting enzyme (ACE) (This patient had a normal chest radiograph). Six cases had undergone a Kveim test; one was positive; this individual had normal serum ACE

Table 4 Haematological and immunological indices for 119 orofacial granulomatosis cases, based on retrievable laboratory reports

Index		*Cases*		*Elevated*		*Low*	
	All	*M*	*F*	*M*	*F*	*M*	*F*
Haemoglobin	102	43	59	–	–	0	6
Erythrocytes	98	46	52	–	–	6	2
Packed cell volume	98	45	53	–	1	9	7
Mean corpuscular volume	99	47	52	5	1	7	3
Mean corpuscular haemoglobin	99	47	52	4	2	4	6
Platelets	96	44	52	–	2	1	–
Total white cells	101	47	54	1	1	1	1
Neutrophils	70	32	38	–	2	–	–
Lymphocytes	70	31	39	–	–	11	14
Monocytes	68	30	38	3	3	1	–
Eosinophils	66	31	35	4	2	–	–
Basophils	58	26	32	–	–	–	–
Ferritin	64	28	36	–	–	3	12
Serum folate	53	25	28	–	–	1	–
Red cell folate	88	40	48	–	–	1	2
B_{12}	93	43	50	–	–	–	–
Albumin	90	45	45	4	–	3	–
Calcium	47	24	23	–	–	2	1
Serum ACE	81	40	41	1	–	–	–
Alkaline phosphatase	61	29	32	7	4	1	1
Kveim test	6	3	3	1	–	–	–
Coeliac antibodies	54	26	28	7	12	–	–
IgE	33	18	15	9	6		
C reactive protein	55	27	28	6	–	2	–
C_1 esterase inhibitor	49	14	35	3	–	2	–

levels. However, no Kveim tests were carried out after 1988. Two of 55 cases (4%) had elevated C-reactive protein levels; both were men. Fifteen of 33 cases (45%) had elevated IgE titres, the majority were men. No less than 19 of 54 cases (35%) had elevated coeliac antibodies; the majority were men. However, these elevated coeliac antibody levels were all in older tests taken near the start of the study period and must be interpreted with caution as titres that would have been considered significant in the 1980s and 1990s might now be considered normal. It is not possible to normalize the titres as the actual tests employed, as well what were regarded as normal values, changed several times during the study period.

Discussion

As stated earlier, we have identified 15 reports of six or more cases of OFG and/or Melkersson–Rosenthal syndrome and/or oral Crohn's disease within the last 30 years (Hornstein, 1973; Tyldesley, 1979; Worsaae *et al*, 1982; Wiesenfeld *et al*, 1985; Ferguson and MacFadyen, 1986; Allen *et al*, 1990; Zimmer *et al*, 1992; van der Waal *et al*, 2002; Handa *et al*, 2003; Mignogna *et al*, 2003; Sciubba and Said-Al-Naief, 2003; El-Hakim and Chauvin, 2004; Sanderson *et al*, 2005; Al Johani *et al*, 2010; Campbell *et al*, 2011), ignoring other, partial reports of some of these series. Details of the findings of these 15 papers are given in Table 5 along with the comparable findings of the present study.

The principal patient complaints and the presenting features in previous studies may, to some extent, reflect the nature of the clinics attended, the referral sources and the interests of the clinicians conducting the studies. Our cases were referred from a variety of sources, and our clinical interest was general rather than restricted to cases that seemed to be oligosymptomatic forms of Melkersson–Rosenthal syndrome or oral manifestations of Crohn's disease.

The reported prevalence of 800/100 000 persons years (Mahler and Kiesewetter, 1996) would seem to us to be improbable. This would give, for example, approximately thirty thousand cases in the Republic of Ireland (or almost half a million cases in the UK).

This is one of the largest series of OFG presented in detail to date. As with all retrospective studies, there is unevenness in the data that can be extracted. In particular, certain tests or observations that were regarded at some time in the 21-year period as relevant were not undertaken or observed at other times. In recent years, biopsy was not routinely carried out on cases with clinical features and history compatible with OFG as it was considered that no other diagnosis was likely. To our knowledge, none of these 119 patients went on to develop Crohn's disease, but there was variability in follow-up.

The sex distribution of our cases was approximately 50:50. This is in accordance with almost all large previous studies, only two of which (Hornstein *et al*, 1987; Handa *et al*, 2003) found any marked imbalance in the sex distribution (see Table 5). Similarly, the median age and range of our cases is similar to most previous studies; however, two studies have reported median ages much lower than ours (Ferguson and MacFadyen, 1986; El-Hakim and Chauvin, 2004), and one has reported a rather greater median age (Sciubba and Said-Al-Naief, 2003) (see Table 5). Our two cases who presented in the ninth decade of life are noteworthy. Women had a statistically significantly older age of presentation. However, when age of onset was examined, there was no significant difference, although age of onset was several years later in women. These findings suggest that onset in women may be later, but that men tend to present for investigation sooner after onset of symptoms.

The predominant clinical finding was lip swelling (91%), which is consistent with previous studies. While fissured tongue is a relatively common condition in the general population, with an estimated prevalence of 6.5% (Axéll, 1976), the high rates reported in Melkersson–Rosenthal syndrome (Worsaae *et al*, 1982; van der Waal *et al*, 2002; Sciubba and Said-Al-Naief, 2003) would suggest that it is a genuine component of the syndrome and hence, possibly, of OFG. Our rate (17%) was almost three times the population normal. Pyostomatitis vegetans is generally regarded as an oral manifestation of inflammatory bowel disease (IBD), particularly ulcerative colitis (Lourenço *et al*, 2010), which makes our finding of 5% prevalence surprising in a group from whom known IBD cases had been excluded. This is perhaps, evidence for viewing OFG as a variant of IBD, or may indicate subclinical bowel involvement in our patients. Our single unexpected clinical finding was the statistically significant heavy male predominance in cobblestoning of the buccal mucous membranes. No previous study has reported this.

There are differences between the symptoms patients complained of at initial presentation and the clinical findings at that time. A small number of patients who complained of lip swelling did not have this feature at first examination. Presumably, this reflects the intermittent nature of the lip swelling in the early stages of the disease (Wiesenfeld *et al*, 1985). Al Johani *et al* (2009, 2010) presented data that permit a similar comparison, in their case between manifestations at disease onset and presenting clinical features in a group of 49 cases. Surprisingly, here the proportion with lip swelling was almost 50% higher in the latter group. In both our patient group and that of Al Johani *et al*, the proportion of patients complaining of oral ulceration was similar to the proportion found to have ulceration on examination, while, unsurprisingly, cobblestoning, tongue fissuring and gingival lesions were found on examination in many patients who had not complained of them.

Almost one-third of our patients reported one or more foods that they felt were related to their condition. Previous foodstuffs reported as causative (as opposed to positive on patch tests or implied from dietary manipulation) are chocolate (Patton *et al*, 1985; Taibjee *et al*, 2004), curry (Patton *et al*, 1985; McKenna *et al*, 1994), cinnamon (Patton *et al*, 1985), wheat products

Table 5 Details of previous studies of orofacial granulomatosis

Paper	*Number of cases*	*Median age at onset (and range)*	*Male/ female ratio*	*Lip swelling*					*Facial swelling*	*Buccal swelling/ cobblestones*	*Gingival involvement*	*Oral ulceration*	*Mucosal tags*	*Fissured tongue*	*Facial paralysis*
				All lip	*Upper lip*	*Lower lip*	*Both lips*	*Lip Unspecified*							
Hornstein *et al* (1987)	73	35–39 (5–70)[a]	28:45	See footnote[b]	35	27			22[c]	3	2			48	20
Tyldesley (1979)	9	16 (10–27)	5:4												
Worsaae *et al* (1982)	33	25 (2–81)	16:17				13	19		22	7			21	6
Wiesenfeld *et al* (1985)	60	20 (3–61)	1:1	41	27	30			28		13	19	12	1	8
Ferguson and MacFadyen (1986)	> 100	15 (3–61)	1∼1												
Allen *et al* (1990)	6	30.5 (19–56)	1:1	6	5	2	2				2				
Zimmer *et al* (1992)	42	33.8[d] (6–73)	1:2	18	14	6	2		11	1	2			0	8
van der Waal *et al* (2002)	13	32.8[d] (15–56)	6:7	13	10	9	6				1			6	3
Sciubba and Said-Al-Naief (2003)	13	47 (22–89)	7:6	10	4	5	2		2	7	3	4	2	5	
Handa *et al* (2003)	13	Not given	9:4	13										3	1
Mignogna *et al* (2003)	19	Not given	Not given	10					5		3				2
El-Hakim and Chauvin (2004)	6	17 (12–52)	1:5	6	2	4	0			1				1	1
Sanderson *et al* (2005)[e]	35	24 (6–74)[f]	17:18	30	17	26				25	24				
Al Johani *et al* (2010)	49	32.4[d] (7–72)	27:22	37	18	28	9		6	15	13	18	4	7	2
Campbell *et al* (2011)	207	23 (2–73)	110:97	184	124	138	77			151	129	53			5[g]
Present study	119	28 (5–84)	57:62	102	69	46	36	2	36	74	35	39	30	18	9[h]

[a]Calculated from figure in text; age given in 5-year age groups.
[b]Data presentation in paper difficult to interpret.
[c]Cheek swelling. Possibly should be regarded as buccal.
[d]Mean age.
[e]These cases may be a subset of Campbell *et al* (2011)
[f]At time of study; median duration from onset was 3 years.
[g]"Five patients … had symptoms consistent with Melkersson Rosenthal syndrome".
[h]From patient histories.

(Patton *et al*, 1985), peanuts (Patton *et al*, 1985), fruit (Patton *et al*, 1985), carbonated drinks (McKenna *et al*, 1994), dairy products (Patton *et al*, 1985; McKenna *et al*, 1994), various alcoholic beverages (Patton *et al*, 1985), fruit (Patton *et al*, 1985) and eggs (Patton *et al*, 1985). Patients have also been reported as implicating toothpaste (Patton *et al*, 1985). Dietary manipulation has implicated very similar groups of substances; toothpaste, chocolate, cinnamon, dairy products, wheat, peanuts, curry and eggs (Haworth *et al*, 1986), monosodium glutamate (Oliver *et al*, 1991) and, possibly, aspartame (Reed *et al*, 1993). The similarity of these findings to our patient group would suggest the need for further careful history, epicutaneous allergy testing and dietary manipulation for all OFG cases. Our own work would suggest that benzoates and cinnamon compounds may be very important allergens (Fitzpatrick *et al*, 2010).

There is very little in the literature on the haematological, biochemical and immunological findings in OFG. As different studies recruited their cases from different sources, variations are to be expected in any case. Studies looking at the oral manifestations of Crohn's disease would be expected to have a number of cases with haematological deficiencies. Studies looking for Melkersson–Rosenthal syndrome might exclude cases that would meet the criteria for an OFG study. Given these probable differences, there may not be great benefit in comparing our laboratory investigations to previously published studies. Campbell *et al* (2011) have recently published details of a large cohort of patients with OFG. However, they included 46 cases with confirmed Crohn's disease, making comparisons with our data difficult.

Tyldesley (1979), in his early series, reported that all cases had had assays of 'the full range of haematological values'. One patient had low iron, and another had both low serum folate and elevated erythrocyte sedimentation rate (ESR). Wiesenfeld *et al* (1985) carried out a wide range of haematological tests on their cases but only reported results for those cases who had a firm diagnosis of Crohn's disease and who could not, therefore, be regarded as typical of OFG cases. Worsaae *et al* (1980, 1982) had haemoglobin, iron studies and ESR results for all of their 33 cases and stated 'no patterns indicating inflammatory activities were observed…' Sanderson *et al* (2005) reported slight anaemia in one of 35 cases; one case had low ferritin. Three cases had low B_{12}, and three cases low folate. It is not stated whether the anaemia and low ferritin were found in the same patient or whether the low B_{12} and folate levels were in the same three cases. Campbell *et al* (2011) reported an abnormal FBC in 23% of patients who would fit our definition of OFG, although details are given only for low haemoglobin (11%). Interestingly, approximately half of their non-Crohn's cases had raised levels of C-reactive protein, compared with only 4% in our series.

Worsaae *et al* (1980, 1982) found that two of their 33 OFG cases (6%) had elevated IgE levels; our figure was 15 of 33 cases tested (45%). This may be consistent with recent work showing the presence in OFG of subepithelial dendritic B cells that express IgE (Patel *et al*, 2010). Nine of our 15 cases with elevated IgE (60%) gave histories of atopy.

When we view our haematological and immunological findings in the light of previous reports, the major differences are the high incidence of elevated alkaline phosphatase levels (18%), low lymphocyte counts and elevated coeliac antibodies. The only previous reports of alkaline phosphatase were of normal levels (Worsaae *et al*, 1980, 1982). There are no previous reports of lowered lymphocyte counts or elevated coeliac antibodies. Our other findings (low erythrocyte counts, packed cell volumes, mean corpuscular volumes, low mean corpuscular haemoglobin levels and lymphocyte counts) have not been reported in any of the previous smaller studies, while low ferritin (or iron) has only occasionally been reported (Tyldesley, 1979; Sanderson *et al*, 2005). The 36% of cases with low lymphocyte counts is particularly striking. We would caution against over interpretation of the coeliac antibody levels; we do not believe that there is good evidence that any of our cases had coeliac disease. If coeliac disease was a significant factor in the aetiology, or a manifestation of the condition, then we would have expected the positive antibody tests to have been spread evenly over the years of the study and not to have been confined to the early years. In fact, none of these cases presented with any other features of coeliac disease.

The one case with a positive Kveim test had normal serum ACE levels. This is consistent with the findings of Wiesenfeld *et al* (1985), whose two cases with positive Kveim tests both had normal serum ACE levels, and with the views of Lindelof *et al* (1985), who were sceptical of a link between OFG and sarcoidosis.

In conclusion, this study presents the demographics, clinical features and investigations of a large cohort of OFG patients. As in previous studies, lip swelling was the most common clinical feature, followed by cobblestoning of the mucous membranes and oral ulceration. Foods were commonly implicated by patients. Most of our patients also had allergy skin tests carried out to common food allergies. The results of those tests have been reported elsewhere (Fitzpatrick *et al*, 2010). It is anticipated that these studies will facilitate prospective studies on the clinical course of OFG and investigation into its aetiopathogenesis.

Having examined the variability in nomenclature (Melkersson–Rosenthal syndrome, OFG, oral Crohn's, granulomatous cheilitis), it is clear that there is a need to standardize the definition of OFG to enable useful collaboration between units and to enable comparison of published studies. This would also facilitate the prospective longitudinal studies that are needed to clarify natural history and treatment outcomes.

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Author contributions

Author Contribution Specifications (if manuscript submitted after implementation of this feature): Professor McCartan, Dr Healy, Dr McCreary, Professor Flint and Professor Rogers were the clinicans responsible for cases and assisted in data retrieval. Dr Toner was the pathologist who reported most of the biopsies. A small number of biopsies were reported by the late Professor DG MacDonald (as acknowledged). Dr McCreary and Dr Healy were responsible for the data base. Professor McCartan and Dr Healy prepared the manuscript with contributions from all other co-authors.

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