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SYSTEMATIC REVIEWS

Association between orofacial granulomatosis and Crohn's disease in children: Systematic review

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Abstract

AIM: To review pediatric cases of orofacial granulomatosis (OFG), report disease characteristics, and explore the association between OFG and Crohn's disease.

METHODS: We conducted a systematic review according to the PRISMA guidelines. We searched Medline, LILACS, Virtual Health Library, and Web of Knowledge in September 2013 for cases of OFG in the pediatric age range (< 18 years), with no language limitations. All relevant articles were accessed in full text. The manual search included references of retrieved articles. We extracted data on patients' characteristics, disease characteristics, association with other diseases, and treatment. We analyzed the data and reported the results in tables and text.

RESULTS: We retrieved 173 reports of OFG in children. Mean age at onset was 11.1 ± 3.8 years (range: 2.0-18 years). Prevalence in males was significant higher than in females (P < 0.001), with a male:female ratio of 2:1. Gastrointestinal signs or symptoms were present in 26.0% of children at the time of OFG diagnosis. Overall, 70/173 (40.4%) children received a concomitant diagnosis of Crohn's disease. In about half (51.4%) of the cases the onset of OFG anticipated the diagnosis of Crohn's disease, with a mean time between the two diagnoses of 13.1 ± 11.6 mo (range: 3-36 mo). Overall, 21/173 (12.1%) of the children with OFG had perianal disease, while 11/173 (6.4%) had a family history of Crohn's disease. Both perianal disease and a family history of Crohn's disease were significantly associated with a higher risk of Crohn's disease diagnosis in children with OFG [relative risk (RR) = 3.10, 95% confidence interval (CI): 2.46-3.90; RR = 2.74, 95%CI: 2.24-3.36, P < 0.0001 for both). Treatment of OFG included steroids (70.8% of children) and other immunosuppressive drugs (42.7%), such as azathioprine, thalidomide and infliximab.

CONCLUSION: High prevalence of Crohn's disease in children with OFG suggests that OFG may be a subtype of Crohn's disease.

Key words: Orofacial granulomatosis; Melkersson-Rosenthal syndrome; Cheilitis granulomatosa; Crohn's disease; Children; Systematic review

Core tip: This systematic review of children with orofacial granulomatosis (OFG) resulted in the following main findings: (1) 40.4% of children with OFG were affected by Crohn's disease during their life; (2) 12.1% of children with OFG had perianal disease; (3) 6.4% had a positive family history for Crohn's disease; (4) both OFG and Crohn's disease were more prevalent in boys; and (5) both diseases had a long-term course, and treatment resembled the treatment used for Crohn's disease. Taken together, these findings suggest that OFG may be a subtype of Crohn's disease.

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INTRODUCTION

The term orofacial granulomatosis (OFG) is conventionally used to describe patients with granulomatous lesions affecting the orofacial tissues[1,2]. The disease is uncommon but is increasingly being recognized. Lip swelling and facial swelling are the most common clinical signs of OFG, often presenting with a spectrum of other features (Figure 1)[3,4]. Over time the majority of patients tend to develop additional lesions, and the lip or facial swelling can become indurated, permanent, and significantly debilitating[1-4].

The pathogenesis of OFG is still uncertain. Different theories suggested a possible role for allergy, infections, and genetic predisposition[1,2].

More recently, it has been hypothesized that OFG may be a subtype of Crohn's disease. This hypothesis is based on the following data: (1) histologically OFG is characterized by noncaseating epithelioid cell granulomas that are indistinguishable from the features of Crohn's disease[1,2]; (2) concurrent intestinal Crohn's disease has been described in 20-50% of adult patients with OFG[5,6]; and (3) both OFG and Crohn's disease have a similar clinical course, that is, long-term with a series of recurrent attacks[1-4].

To the best of our knowledge, no systematic review of pediatric cases of OFG has previously been published. The objective of this work was to systematically review pediatric cases of OFG, and evaluate the association between OFG and Crohn's disease.

MATERIALS AND METHODS

This systematic review was conducted according to the PRISMA guidelines[6]. We searched Medline, LILACS, Virtual Health Library, and Web of Knowledge in September 2013 for cases of OFG in the pediatric age range (< 18 years), with no language limitations. The search strategy is reported in Table 1. All relevant articles were accessed in full text. The manual search included references of retrieved articles. We extracted data on patients' characteristics, disease characteristics, association with other diseases, and treatment. We analyzed the data and reported the results in the tables and text. Cases of granulomatous perioral dermatitis, Melkersson-Rosenthal syndrome (*i.e.*, cases characterized by facial nerve palsy), and OFG-like lesions after organ transplant were excluded from this review.

RESULTS

The process of study selection is reported in Figure 2. We retrieved 18 case series[7-23] and 35 case reports[24-56], for a total of 173 children with OFG. One article could not be found in full text[57].

The mean age at OFG onset was 11.1 ± 3.8 years (range: 2.0-18 years). Although not all reports detailed the sex of the patients, OFG appeared to be significantly more prevalent in boys than in girls ($P < 0.001$, Table 1), with a male to female ratio of 2:1. The disease was reported more commonly in children of Caucasian origin.

The primary clinical feature of children with OFG was lip swelling (93.3%), with involvement of either one or both lips (Table 2). About half of the children presented some intraoral manifestations, such as ulcers, gingival hyperemia or hypertrophy, oral cobble-stoning lesions, or tongue abnormalities. Both angular cheilitis and perioral swelling were each present in about 20% of children. Gastrointestinal signs or symptoms (perianal disease, and/or abdominal pain, diarrhea, or intestinal bleeding) were present in 26.0% of the cases at time of OFG diagnosis.

The diagnosis of OFG was made more often by a team comprising different specialists (65.3%), rather than by one single type of physician (24.7%, $P < 0.001$, Table 3). Stomatologists and dentists were the specialists who were more frequently involved in the diagnosis of OFG (64.7%), followed by gastroenterologists (49.7%), while dermatologists and pediatricians were involved in the diagnosis in only 22.0% and 18.5% of cases, respectively. A consistent delay (months to years) in reaching the final diagnosis of OFG was frequently reported, with a single patient reporting up to 5 years delay[18,42,52].

Differential diagnosis of Crohn's disease was considered in 79.2% of children, while sarcoidosis and tuberculosis were investigated in 20.8% and 14.4% of cases, respectively. Crohn's disease was diagnosed in 70/173 (40.4%) children with OFG, either at time of presentation of OFG, or during the following months or years (mean time: 13.1 ± 11.6 mo, range: 3-36 mo). In contrast, only three children (1.7%) were diagnosed with tuberculosis[33-35], two (1.1%) with sarcoidosis[16], and 19 (10.9%) with allergy/atopy.

Overall, 21/173 (12.1%) of the children with OFG had perianal disease, while 11/173(6.4%) had a family history of Crohn's disease. Both perianal disease and a family history of inflammatory bowel disease were significantly associated with an increased risk of Crohn's disease in children with OFG [relative risk (RR) = 3.10, 95% confidence interval (CI): 2.46-3.90; RR = 2.74, 95%CI: 2.24-3.36, $P < 0.0001$ for both, Table 4].

There was heterogeneity in the reported incidence of Crohn's disease and of perianal disease among different case series, with those reported by gastroenterologists[7,11], describing a significantly higher incidence of Crohn's disease than other series. In Campbell *et al*[7], the largest OFG case series available including both adults and children (207 patients, of which 22% were children), the incidence of Crohn's disease was similar in children and adults with OFG, but in children the occurrence of OFG anticipated the onset of Crohn's disease significantly

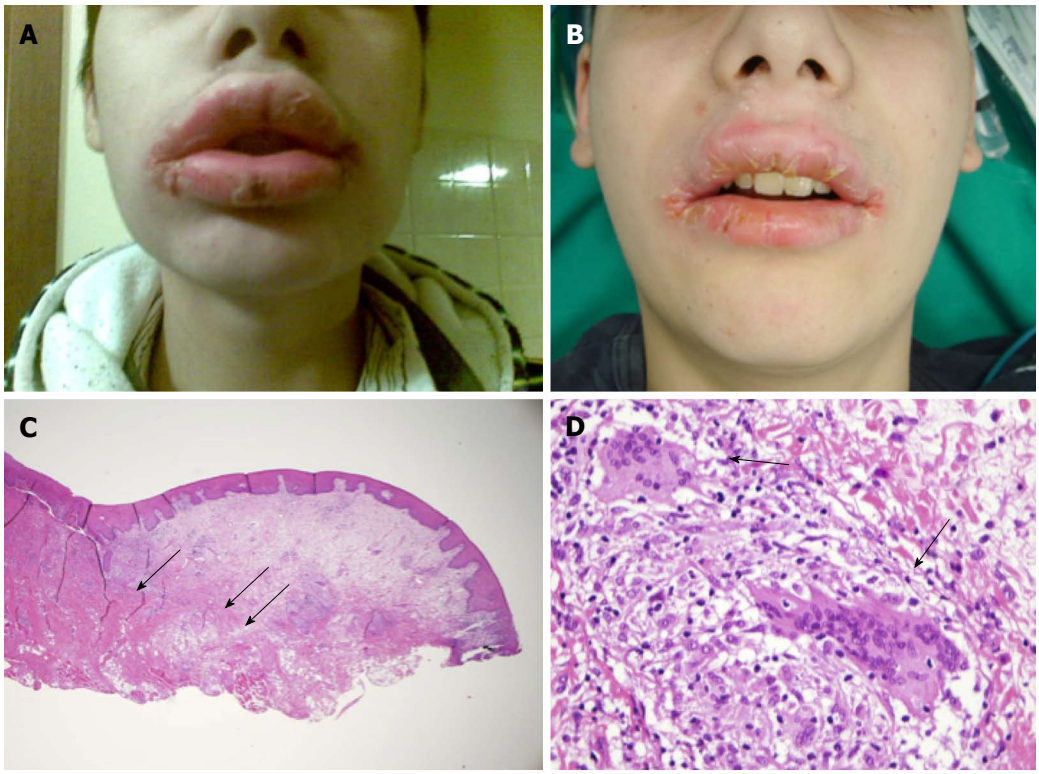

Figure 1 Case 1, swelling of both lips and gingival lesions (A and B); Histological examination showing typical noncaseating granulomas (arrows) and inflammatory infiltrate (C and D).

Table 1 Demographic characteristic of children with orofacial granulomatosis *n* (%)

Patient characteristics	Value (*n* = 173)	*P* value
Age, mean ± SD (range, yr)	11.1 ± 3.8 (2-18)	
Sex		
Male	69 (39.9)	< 0.001[1]
Female	34 (19.6)	
Unspecified	70 (40.5)	
Ethnic group		
Caucasian	19 (11.0)	< 0.001[1]
African	3 (1.7)	
Indian	2 (1.2)	
Unspecified	149 (86.1)	

[1]Indicate similarities with Crohn's disease.

more often than in adults (84% *vs* 27%, $P = 0.0003$)[7]. Ulcers and raised C-reactive protein were more frequent in patients with OFG and Crohn's disease than in those with OFG alone (respectively 49% *vs* 15%, $P = 0.001$ and 73% *vs* 49%, $P = 0.01$)[7]. Cases with intraoral involvement, perianal disease and intestinal Crohn's disease were more likely to occur in those with childhood onset of OFG compared to those with adult onset (44% *vs* 24%, $P = 0.09$)[7].

When Crohn's disease was diagnosed in children with OFG, oral and perioral lesions were not considered a metastatic manifestation of Crohn's disease, but an expression of the disease in the digestive tract.

Although the duration of follow-up was short in most reports, overall, 26.4% and 17.6% of children received two and three or more treatment attempts, respectively (Table 5). A combination of two or more drugs in the same treatment attempt was reported in 53.7% of children. Steroids were prescribed in 70.8% of children. Other immunosuppressive or immunomodulatory drugs were administered to 42.7% of children, and among these, azathioprine/6-mercaptopurine (6MP; 12.3%), thalidomide (10.1%) and infliximab (9.1%) were the most frequently prescribed. Eight (9.1%) children underwent surgery.

DISCUSSION

This review of the pediatric literature highlights the fact that OFG is a disease that can occur during childhood and adolescence. The exact prevalence of the disease in children is unknown, and cannot be derived from this review. Reports from specialized centers suggest that the real prevalence of the disease may be higher than what has been reported so far in the literature[7]. Results from the present review also suggest that OFG in children is still not a well-known disease among physicians, and that there is uncertainty in respects to its diagnosis, with possible diagnostic delay.

This review highlights some important findings regarding Crohn's disease and OFG. First, Crohn's disease was diagnosed in 40.2% of children with OFG. This rate could be underestimated due to several factors: (1) Crohn's disease was not systematically assessed in all children with OFG; (2) on average, children were followed

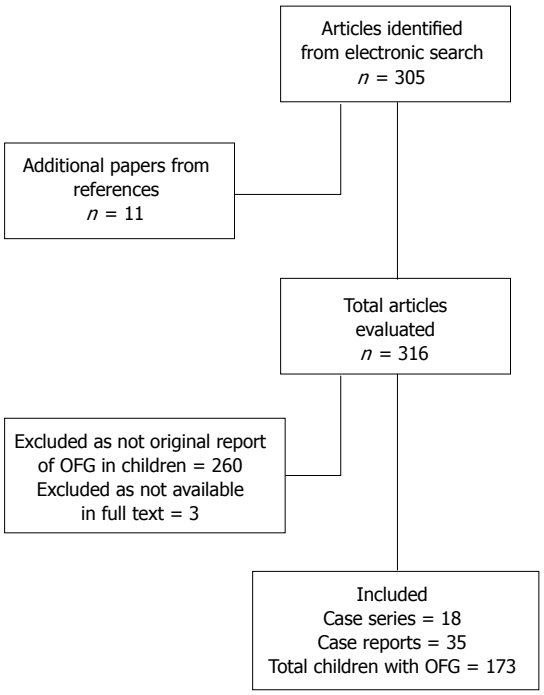

Figure 2 Flow diagram of studies selection. OFG: Orofacial granulomatosis.

up for a short time, while this review highlights that gastrointestinal signs and symptoms may appear at a later stage (on average, 13 mo later); (3) Crohn's disease may be subclinical or silent, as observed in reports in adults, showing that a considerable percentage of patients with OFG without intestinal symptoms were diagnosed with Crohn's disease after ileoscopy or radiolabeled white cell screening[58]; (4) patients with OFG were treated with steroids or other immunosuppressive drugs that could have silenced the intestinal symptoms of Crohn's disease; (5) publication bias may have affected the characteristics of reported cases; and (6) there is some confusion between the diagnosis of OFG and oral Crohn's disease[59], and this may have affected the number of cases reported as OFG. Although some of the above-mentioned factors may have affected the prevalence of Crohn's disease in OFG by overestimating it, most factors may have led to an underestimation of the actual prevalence of Crohn's disease in OFG.

Second, 6.4% of children with OGF also presented a family history of inflammatory bowel disease. Such a percentage is much closer to what is reported in the population with Crohn's disease, than in those not affected by inflammatory bowel disease. Perianal disease, which is already a recognized subset of Crohn's disease, was detected in 12.1% of children with OFG overall. Intra-oral lesions and perianal disease often occur together in Crohn's disease[60], and cohort studies have showed that both manifestations are important predictors of Crohn's disease severity[59,60].

Third, this review highlights other similarities between Crohn's disease and OFG: both OFG and Crohn's disease[58-60] are more prevalent in boys; both diseases have a

Table 2 Clinical manifestations in children diagnosed with orofacial granulomatosis *n* (%)

Clinical features	Value (*n* = 104)[2]
Lips	
Present	104 (100.0)
Lip swelling	97 (93.3)
Only upper lip	27 (26.0)
Only lower lip	15 (14.4)
Both lips	26 (25.0)
Preset but unspecified	29 (27.9)
Angular cheilitis	22 (21.1)
Intra-oral manifestation[1]	
Present	50 (48.1)
Oral ulcerations	24 (23.1)
Gingival hyperemia/hypertrophy	22 (21.1)
Tongue abnormalities	8 (7.7)
Oral cobble-stoning lesions	8 (7.7)
Facies	
Perioral/cheek swelling	19 (18.3)
Neck	
Cervical lymphadenopathy[1]	6 (5.8)
Gastrointestinal	
Present	27 (26.0)
Perianal disease[1]	21 (20.2)
Abdominal pain[1]	7 (6.7)
Diarrhea[1]	7 (6.7)
Intestinal bleeding[1]	6 (5.8)
Nutritional status	
Impaired growth[1]	5 (4.8)
Obesity	1 (1.0)
Ocular	
Conjunctivitis[1]	1 (1.0)
Genitalia	
Vulvar oedema[1]	2 (2.0)
Scrotal swelling[1]	1 (1.0)

[1]The asterisks indicate similarities with Crohn's disease; [2]All cases with a detailed description of clinical signs and symptoms are reported in the table.

long-term course; and treatments used for OFG resemble those used for Crohn's disease. Even the list of other diseases diagnosed in association with OFG (*i.e.*, erythema nodosum, and alopecia), although the number of cases was limited, resembles the list of immunological diseases usually associated with Crohn's disease.

All the above findings suggest that OFG and Crohn's disease may be two variants, if not just two different localizations, of the same chronic inflammatory disease. Other authors have proposed this hypothesis, based on the high (20%-50%) reported prevalence of Crohn's disease in adults with OFG[5,6].

To the best of our knowledge no systematic review of adult cases of OFG has been carried out so far, and cases reported in adults suffer from the same risk of bias as cases reported in children (*e.g.*, short follow-up time). More studies in an adequate sample of patients with OFG (both children and adults) with a systematic evaluation for Crohn's disease and long follow-up time are needed to explore further the hypothesis that OFG is a subtype of Crohn's disease or even one of its manifestations.

So far, based on existing literature, Crohn's disease

Table 3 Diagnostic process in children reported with orofacial granulomatosis *n* (%)

Characteristics	Value (*n* = 173)
Physicians involved in the diagnosis	
Stomatologist/dentist/maxillo surgeon	112 (64.7)
Gastroenterologist	86 (49.7)
Dermatologist	38 (22.0)
Pediatrician	32 (18.5)
Otorhinolaryngologist	13 (7.5)
Allergologist	4 (2.3)
Plastic surgeon	3 (1.7)
Internal Medicine	1 (0.6)
Composition of the team	
One single specialty	60 (34.7)
More than one specialty	113 (65.3)
Differential diagnosis considered at time of OFG presentation	
Crohn's disease	137 (79.2)
Sarcoidosis	36 (20.8)
Tuberculosis	25 (14.4)
Allergy	19 (11.0)
Infection	17 (9.8)
C1q esterase deficiency	10 (5.8)
Melkersson–Rosenthal syndrome	4 (2.3)
Autoimmunity	3 (1.7)
Vasculitis	1 (0.6)
Foreign body	1 (0.6)
Enteropathic acrodermatitis	1 (0.6)

OFG: Orofacial granulomatosis.

Table 4 Concomitant diseases diagnosed in children with orofacial granulomatosis and associated characteristics *n* (%)

Disease	Value (*n* = 173)	RR (95%CI), *P*
Crohn's disease		
Total children	70 (40.4)	
At presentation	34 (19.6)	
During follow-up	36 (20.8)	
Time from OFG diagnosis to Crohn's diagnosis (mean ± SD, range)	13.1 ± 11.6 (3-36)	
Presence of perianal disease		
Total	21/173 (12.1)	3.10
In children with Crohn's	21/70 (30.0)	(2.46-3.90),
In children without Crohn's	0/103 (0)	0.0001
Familiarity for inflammatory bowel diseases		
Total	11/173 (6.4)	2.74
In children with Crohn's	11/70 (15.7)	(2.24-3.36),
In children without Crohn's	0/103 (0)	0.0001
Allergy/atopy		
Any allergy	19 (10.9)	
Asthma	7 (4.0)	
Atopy	6 (3.5)	
Rhinitis/rhinoconjunctivitis	6 (3.5)	
Eczema	6 (3.5)	
Hives	1 (0.6)	
Other diagnosis		
Tuberculosis	3 (1.7)	
Sarcoidosis	2 (1.1)	
Other diseases	10 (5.7)	
Erythema nodosum	3 (1.7)	
Insulin dependent diabetes	1 (0.6)	
Celiac disease	1 (0.6)	
Alopecia	1 (0.6)	
Low CD4/CD8 ratio	1 (0.6)	
Epilepsy	1 (0.6)	

Table 5 Treatments of children with orofacial granulomatosis *n* (%)

Treatment characteristics	Value (*n* = 104)[1]
A treatment was prescribed[2]	
Yes	89 (96.7)
No	3 (3.2)
Unspecified	12 (11.5)
Number of treatment attempts reported[2]	
One	38 (55.8)
Two	18 (26.4)
Three or more	12 (17.6)
Unspecified	21 (23.5)
More than one drug in the same treatment attempt[2]	
Yes	36 (53.7)
No	31 (46.2)
Unspecified	22 (24.7)
Type of treatments prescribed[2]	
Antibiotics	26 (29.2)
Anti-histaminic	10 (11.2)
Steroids-total	63 (70.8)
Topical	27 (30.3)
Intralesional	24 (27.0)
Oral	39 (43.8)
Other immunosuppressive-total	38 (42.7)
Azathioprine/6MP	11 (12.3)
Thalidomide	9 (10.1)
Infliximab	8 (9.0)
Dapsone	4 (4.5)
Tacrolimus (topic)	4 (4.5)
Methotrexate	3 (3.4)
Tacrolimus (systemic)	3 (3.4)
Hydroxychloroquine/chloroquine	2 (2.2)
Colchicine	2 (2.2)
Other treatments	
5ASA	13 (14.6)
Chlorhexidine (topic)	4 (4.5)
Enteral nutrition	2 (2.2)
Fumaric acid esterase	1 (1.1)
Surgery	8 (9.0)

[1]All cases that provided a detail description of clinical signs are reported in the table; [2]Percentages are calculated on the number of children for which the treatment was specified. 5-AZA: 5-aminosalicylic acid.

should be considered in the differential diagnosis of every child with signs of OFG; in particular, if other signs of systemic, gastrointestinal or perianal involvement are present. If Crohn's disease is not diagnosed at the time of OFG presentation, patients with OFG should be closely followed up for any sign of intestinal Crohn's disease, including perianal disease.

If OFG and Crohn's disease are two different clinical entities, more precise diagnostic criteria should be developed to differentiate between the two diseases.

In conclusion, OFG has been considered a different entity from Crohn's disease due to its presentation (lip and buccal involvement) and to the absence of systemic signs and symptoms[1-5]. The findings of our systematic review on children with OFG suggest that OFG may be a subtype of Crohn's disease. Mores studies with a systematic evaluation of patients and with adequate follow-up are needed to confirm this hypothesis. Based on the existing evidence, Crohn's disease should be considered

in the differential diagnosis of children with unexplained OGF. These children should be also followed up in the long term, because intestinal Crohn's disease may develop after several years.

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COMMENTS

Background

The term orofacial granulomatosis (OFG) is conventionally used to describe patients with granulomatous lesions affecting the orofacial tissues. So far, OFG had been considered a different entity from Crohn's disease, although the hypothesis that OFG may be a subtype of Crohn's disease has been proposed.

Research frontiers

To the best of our knowledge, no systematic review of pediatric cases of OFG has previously been published. The objective of this study was to review systematically all pediatric cases of OFG, report on the disease characteristics, and evaluate the association between OFG and Crohn's disease.

Innovations and breakthroughs

Crohn's disease was diagnosed in approximately 40% of children with OFG, either at time of presentation of OFG, or during the following months or year (mean time: 13.1 ± 11.6 mo, range: 3-36 mo). Such a high prevalence of Crohn's disease in children with OFG, and other common features between the two diseases, suggest that OFG may be considered a subtype of Crohn's disease.

Applications

Crohn's disease should be considered in the differential diagnosis of children with OFG. Children with OFG should be also followed up in the long term, because intestinal Crohn's disease may develop after several years.

Terminology

OFG is a rare granulomatous disease that affects the orofacial tissues. Lip and facial swelling are the most common clinical signs, often presenting with a spectrum of other features. Over time the majority of patients tend to develop additional lesions, and the lip or facial swelling can become indurated, permanent, and significantly debilitating.

Peer review

This is a well-documented review article regarding the association between OFG and Crohn's disease in children.

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