The role of exclusive enteral nutrition in the management of orofacial granulomatosis in children

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Background: **Orofacial granulomatosis (OFG) is a term used to describe a persistent, painless swelling of lips and orofacial region. It can be associated with ulceration, gingival hypertrophy and cobble stone appearance of the buccal mucosa. OFG is commonly associated with Crohn's disease and can precede the intestinal manifestation of the disease. Exclusive enteral nutrition (EEN) is a recognized treatment for induction of remission for Crohn's disease. The aim of this study was to review the use of EEN in the management of OFG in children.**

Methods: **Retrospective review of medical records of all children diagnosed with OFG between 2007 and 2012 was conducted. Presence of comorbidities, progression to inflammatory bowel disease (IBD) and response to EEN was evaluated.**

Results: **Twenty-nine children were included, mean age at diagnosis was 9 years (standard deviation 3.9) years. Ten children had isolated OFG and 19 had OFG and IBD, of which 12 presented with OFG and IBD and 7 developed IBD later. Median time to progression to IBD was 33 months (inter quartile range: 9.8-85.5). Twenty-two children completed 6 weeks of EEN, and 19 showed clinical improvement in the OFG appearance.**

Conclusion: **EEN appears to be an effective treatment option for children with isolated OFG or OFG and IBD.**

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Key words: **gastroenterology;**
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Introduction

Orofacial granulomatosis (OFG), also known as cheilitis granulomatosa, is a term used to describe a persistent, painless swelling of lips and orofacial region.[1] It can be associated with ulceration, gingival hypertrophy and cobblestone appearance of the buccal mucosa.[2] The underlying histology is characterized by non-caseating granulomatous inflammation.[3]

The term OFG was first used by Wiesenfeld et al in 1985 to describe patients with orofacial swelling which included the previously recognised Melkersson Rosenthal syndrome and cheilitis granulomatosa with distinct histological feature that is similar to Crohn's disease and systemic sarcoidosis.[1] Although it is commonly associated with Crohn's disease,[4] there are a number of disorders that may present with recurrent or persistent lip and orofacial swelling such as tuberculosis,[5] sarcoidosis,[6] contact dermatitis[7] and allergies.[1] Some authors considered OFG as diagnosis of exclusion after other systemic disorders causing granulomatous inflammation are reliably excluded.[8]

Crohn's disease, a transmural granulomatous inflammation of the gastrointestinal tract, can have a distinct oral and labial manifestation grouped together under the term oral Crohn's disease (OCD). It can precede the diagnosis of Crohn's disease.[9] Although OCD and OFG can share some clinical features; including indistinguishable histological feature, a remitting and relapsing course and clinical response to similar medications, the association between the two is poorly understood.[4] It has been reported that as high as 50% of children with OFG will develop Crohn's disease.[4,10] However, it may take up to few years to develop clinical features of Crohn's disease in children with OFG.[9] A recent systematic review of children with OFG suggest that OFG may be a subtype of Crohn's disease.[4]

There are different treatment modalities described for the management of OFG including systemic and intra lesion steroid,[11] thalidomide,[12] infliximab[13] and various types of dietary exclusion with variable response rate.[14] There are limited data to support one

management option as the evidence is largely confined to isolated case reports and small case series.

Exclusive enteral nutrition (ENN) using polymeric or elemental liquid diet is a recognised treatment for induction of remission in pediatric Crohn's disease with a reported success rate of up to 88%.[15-17] Whilst polymeric and elemental liquid diets are thought to be equally effective treatment modalities for Crohn's disease, it is accepted that elemental diet is the preferred option in children with clinically diagnosed allergy.[15] EEN with elemental liquid diet was successfully used in the treatment of children with OFG and Crohn's disease.[18]

In our institution, we offer EEN as the first line therapy for children with OFG in recognition to the strong interlink between OFG and Crohn's disease. In this study, we aimed to review the use of EEN in the management of OFG in children in our institution, a tertiary pediatric gastroenterology centre.

Methods

The project was registered in the Research and Development Office at Great Ormond Street Hospital. However, full ethic approval was not required. All children diagnosed with OFG in the department of pediatric gastroenterology at Great Ormond Street Hospital London between 2007 and 2012 were identified by searching a medical database where electronic patient records were kept. Diagnostic criteria for OFG were the presence of recurrent or persistent lip swelling that may have been associated with oral ulcers, gingival hypertrophy and appearance of cobblestone of the buccal mucosa.[1]

A total number of 29 patients with clinically diagnosed OFG were identified. The initial presenting symptoms of children with OFG and Crohn's disease outside the study period were assessed and time of progression (if applicable) from OFG to Crohn's disease was calculated and included in the analysis. All children had some gastrointestinal complaints and underwent an upper endoscopy and ileocolonoscopy at presentation to assess the presence of inflammatory bowel disease (IBD). Small bowel imaging was performed if there was a clinical suspicion of IBD. Inflammatory markers, immunoglobulin E (IgE), radioallergo-sorbent test (RAST) and peripheral blood eosinophil counts were measured at presentation.

Management of Crohn's disease followed internationally recognised guidelines for induction and maintenance of remission.[16] EEN is the first line for induction of remission in our institution. All children presenting with OFG were offered 6 weeks of EEN using an amino acid based formula (Elemental E028©). Response was monitored closely. Clinical response was assessed by measuring disease activity index in Crohn's disease[16] and disappearance of lip swelling in children with OFG. Unfortunately, faecal calprotectin was not available at our institution during the study period.

Food reintroduction after completion of ENN was supervised by a dietician and further dietary exclusion was decided by clinical assessment of adverse food reaction, with special emphasis paid to dairy, soya, wheat, gluten and eggs. EEN was used as the sole agent for induction of remission. Children who failed to respond, EEN was discontinued and another therapy was instituted.

ENN compliance was supervised and follow up was carried out by pediatric dietician, while clinical response was assessed by the medical team.

Background information and baseline characteristic were assessed by descriptive statistic. Results were expressed as mean (±standard deviation), median (25-75% inter-quartile range, IQR) or mean (95% confidence interval, CI), as appropriate.

Results

Twenty nine children (19 males and 10 females) with clinically diagnosed OFG were identified. Mean average age at presentation (±SD) was 9 years (±3.9). Ten children (34%) had an isolated OFG (normal endoscopy), while 19 (66%) were OFG and IBD. Seven children presented initially with OFG then progressed to IBD, the median time of progression from OFG to IBD was 33 months (IQR 9.8-85.5) ranging from 4 months to 144 months. Fourteen (48%) children had normal serum IgE level at diagnosis (normal values in our institution is 0-41 kU/L) and 15 (52%) had high levels. Twenty-one (72%) had normal eosinophil count at presentation, six (21%) had a low level and two (7%) had a high eosinophil count. Specific IgE testing of food items were negative in 23 (79%) children at diagnosis, four (14%) of children had positive Specific IgE for dairy, four (14%) were positive for soya, two (7%) were positive for wheat and one (3%) was positive for egg. Skin prick test or allergy patch were not available at our institution at the time of the study. Median erythrocyte sedimentation rate (ESR) at diagnosis was 18 (IQR 8.3-47.8). Eight children had a lip biopsy, they all showed nonspecific inflammation and four showed granulomatous inflammation.

Twenty-two (76%) children completed 6 weeks of EEN, four (14%) had systemic steroids, one (3%) had intra-lesional steroid injection and two (7%) had targeted exclusion diet based on clinical history and elevated serum specific IgE for food items. Maintenance

Table. Background and demographic information

Parameters	Value
Total number of children	29
Males/Females	19/10
Age at presentation (y), mean (±SD)	9.1 (±3.9)
Pattern, *n*	
Isolated OFG	10
OFG and IBD	19
OFG progressed to IBD	7
Time to develop IBD (mon)	
Median (IQR)	33 (9.8-85.5)
Range	4-144
ESR at presentation, median (IQR)	18 (8.3-47.8)
Total IgE at presentation, *n* (%)	
Normal (0-41 kU/L)	14 (48%)
High	15 (52%)
Eosinophil count at presentation, *n*	
Normal	21
Low	6
High	2
RAST, *n*	
Negative	23
Positive for:	
Dairy	4
Soya	4
Wheat	2
Egg	1
Children completed EEN	22
Clinical improvement	19
Other therapy	7
Clinical improvement	3
Lip biopsy	8
Maintenance therapy	
Azathioprine	23
5ASA	7
Prednisolone	4
Intra lesion steroids	1
Infliximab	1

RAST: radioallergosorbent test; IQR: inter quartile range; SD: standard deviation; OFG: orofacial granulomatosis; IBD: inflammatory bowel disease; ESR: erythrocyte sedimentation rate; 5ASA: 5-aminosalicylates.

therapy is listed in the Table.

All 10 children with isolated OFG received 6 weeks of EEN and all showed clinical improvement as defined by improving visual appearance of the lips. Of 19 children with OFG and IBD, 12 were able to complete 6 weeks of ENN, 10 improved clinically as demonstrated by reduction in disease activity index and visual improvement of the lips.

Discussion

OFG is a rare granulomatous disease that affects the oral and maxillofacial region. It is characterized by lips and facial swelling.[1,2] The overall incidence of pediatric OFG is rising. Although the initial definition of OFG excludes clinical intestinal disease[9] up to half of the patients will have intestinal inflammation without the presence of gastrointestinal symptoms.[4] The resulting facial disfigurement can lead to significant psychological distress. In this cohort 12 (41%) children had inflammatory bowel disease at presentation with a further 41% (7 children out of the remaining 17) progressed to develop IBD.

Management of IBD follows internationally recognised protocols; however there is no consensus regarding management of OFG. Different modalities of treatment are described in the literature including intralesion and systemic steroids, immunosuppressant, thalidomide, topical tacrolimus and surgical resection,[19] all of which were case reports or small case series with variable outcome. Although sharing a similar clinical feature with oral allergy syndrome (an acute form of orofacial swelling after contact with a raw plant food), dietary exclusion in OFG is reported to be ineffective.[14]

Like most other disorders that affect the orofacial area, OFG has a strong allergy basis with atopy reported in as high as 60% of OFG patients.[20] Diet exclusion is often the first line therapy. White et al[20] reported clinical improvement with 8 weeks avoidance of cinnamon and benzoate, while Oliver et al[21] reported symptoms improvement following elimination of monosodium glutamate.

The association between atopy and Crohn's disease is not clear. Patel et al[22] reported a higher incidence of atopy in patients with Crohn's disease than controls and high atopy rate in patients with OFG and Crohn's disease. In this study, 86% of children improved after 6 weeks of EEN using amino acid formula. The success rate is high and is closer to previous reports of induction of remission in pediatric Crohn's disease using EEN. Thirty seven percent of children who initially presented with OFG (7 out of 19 children) went on to develop Crohn's disease, raising a question whether pediatric OFG is a pre-IBD condition. The need for long term follow up is required for those groups of patient as disease progression can be very slow. In this study the range of progression from OFG to Crohn's was 4 months to 144 months, indicating the need for long term follow up of children with OFG. The appearance of gastrointestinal symptoms in children with OFG warrants detailed assessment and consideration of endoscopy.

Subepithelial dendritic B cells are identified as key players in developing oral immune response with a high level of expression of IgEs in patients with OFG,[23] but the direct involvement of allergy in the pathology of OFG is yet to be proven. 52% of our population had high total IgE at presentation, however dietary screening for common food allergens were largely negative (in 79% of children).

For maintenance therapy, children with Crohn's

disease followed the recognised management protocol while children with isolated OFG were mainly maintained on exclusion diet based on laboratory (specific IgE levels for food allergens) and clinical responses.

This study has a number of limitations; it is a retrospective data collection over long period of time and the diagnosis of OFG was based on clinical feature (only 8 children had lip biopsy for histological confirmation). Also sensitive parameters to detect early IBD (such as faecal calprotectin) were not available. Another limitation is the absence of skin prick test and patch test which were not routinely performed at our institution at the time of the study. However, our data has showed clinical improvement in the appearance of OFG (albeit with no photographic follow up) in children treated with 6 weeks EEN, a well-structured clinical trial is required to further understand this disfiguring and poorly understood disorder.

In this pediatric cohort, OFG in children appears to show good clinical response to ENN and subsequent exclusion diet. 37% of patients went on to develop Crohn's disease, some as late at 12 years after the initial diagnoses of OFG. It is paramount that children with OFG are offered long term follow up and the presence of gastrointestinal symptoms should be promptly investigated.

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Competing interest: None.
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