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**OROFACIAL GRANULOMATOSIS AND ORAL SYMPTOMS IN A SOUTH
AUSTRALIAN PAEDIATRIC POPULATION WITH CROHN'S DISEASE**

DOCTOR OF CLINICAL DENTISTRY (Paediatric Dentistry)

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Thesis Declaration

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Evelyn Kar-Yun Yeung

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List of Abbreviations

APAIBDD	Australian Paediatric and Adolescent Inflammatory Bowel Disease Database
ASCA	<i>anti-Saccharomyces cerevisiae</i> antibodies
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CG	Cheilitis granulomatosa of Miescher
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
MRS	Melkersson Rosenthal syndrome
OCD	Oral Crohn's disease
OFG	Orofacial granulomatosis
p-ANCA	Perinuclear-staining antineutrophil cytoplasmic antibodies
PDU	Paediatric Dental Unit
WCH	Women's and Children's Hospital, Adelaide, South Australia

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Abstract

This research is a pilot study to determine if oral manifestations, including orofacial granulomatosis (OFG) are a precursor to, or an oral manifestation of paediatric Crohn's Disease (CD), or a separate pathological condition in a South Australian paediatric population. Additionally the investigation and management of two paediatric patients who first presented with oral symptoms and diagnosed with CD is reported.

Retrospective analysis was conducted on patients on the Australian Paediatric and Adolescent Inflammatory Bowel Disease Database and the medical records of patients with CD or OFG from the Paediatric Dental Unit, Women's and Children's Hospital (n=945). From this group, a cohort of 22 eligible South Australian paediatric patients participated in a prospective clinical study. Over a period of 14 months questionnaires and clinical assessments were conducted. Data collection included patient/parent questionnaire, clinical examination, clinical photography and serological investigation. Of the cohort of 22 paediatric patients with CD assessed, 54.5% of patients presented with oral involvement. The mean age of CD diagnosis was 11 years and 4 months, while the mean age of OFG diagnosis was 9 years and 6 months.

A retrospective analysis was conducted of oral and gastrointestinal biopsies from 8 paediatric patients who had had a provisional diagnosis of OFG and for whom subsequent investigation for CD was undertaken. The histopathological features of oral and gastrointestinal lesions in each patient were compared. Of the 8 patients assessed, 6 were diagnosed with OFG on the basis of the oral biopsies. Only 1 patient had both macroscopic and microscopic changes consistent with active CD and all 6 patients with OFG had perianal disease. A

multidisciplinary approach to investigating all relevant clinical, histological and serological information resulted in 7 of the 8 patients having a final diagnosis of CD.

The results from this study indicate that oral involvement maybe more common than the national data indicates and that it may both precede and be an oral manifestation of CD. From the histological investigation of oral and gastrointestinal biopsies there is no conclusive evidence found linking OFG and CD, however given the strong association between the two conditions and other clinical and serological markers, multidisciplinary management is recommended to establish a definitive diagnosis. Data obtained from the prospective clinical assessment and clinical photography was used to devise a visual OFG/oral CD diagnostic guide. This was developed to aid in the diagnosis of OFG and oral CD by medical and dental practitioners. The results from this study also indicate the importance of collaboration of dental and medical physicians to aid in early diagnosis and management of CD.

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Thesis Format

This thesis presents the three different investigations in this study un-formatted articles which are intended for publication following submission of this thesis. Each article is presented individual chapters.

The introductory chapter discusses the background of OFG and CD, the null hypothesis, objectives of this research, specific aims and the link between the different investigations undertaken in this study.

The second chapter reviews the literature of OFG and CD to discuss the aetiology, clinical presentation, investigation, histopathology, and clinical management of CD and OFG.

The third chapter describes the main investigation from this study involving retrospective analysis of data and findings from questionnaires and clinical assessments

The fourth chapter details the findings from the retrospective histopathological analysis of oral and GI biopsy specimens in 8 patients.

The fifth chapter consists of a case report of two paediatric patients who initially presented with both orofacial and gastrointestinal symptoms. Multi-disciplinary investigations were under taken and the management of the oral symptoms was reviewed.

The final chapter discussed the major finding from the three investigations and their significance, problems that were encountered and potential future research based on the findings in this study.

All references are listed at the end of the thesis, and tables and figures with their corresponding text are presented together where possible.

Chapter I

Introduction

Orofacial granulomatosis (OFG) is the term given to describe noncaseating granulomatous disorders and lymphoedema involving oral and maxillofacial soft tissues. It is considered to be an uncommon disorder (Leao, Hodgson et al. 2004) with increasing recognition and debate regarding associated nomenclature, as well as implications and relation to other disease processes (Tilakaratne, Freysdottir et al. 2008).

OFG encompasses varying characteristics from oral Crohn's disease (OCD), oral sarcoidosis, Melkersson Rosenthal syndrome (MRS) and cheilitis granulomatosa (CG) of Miescher (Tilakaratne, Freysdottir et al. 2008). Numerous disorders may present with persistent and/or recurrent labial enlargement and intra oral swellings that have a similar histopathological feature of noncaseating granulomas (Bogenrieder, Rogler et al. 2003; Leao, Hodgson et al. 2004). Therefore it is important that a correct diagnosis is established in order to facilitate prompt and appropriate systemic therapy to manage the associated signs and symptoms and associated systemic manifestations of the disease (Leao, Hodgson et al. 2004; Rowland, Fleming et al. 2009).

A definitive aetiology has not been established for OFG. Its incidence is linked to food substances, food additives, dental materials, various microbiological agents and other systemic inflammatory disorders (Leao, Hodgson et al. 2004; Tilakaratne, Freysdottir et al. 2008). Galbraith *et al.* (2005) found that inflammatory bowel diseases (IBD) are a common aetiology for persistent oral lesions in the paediatric population (Galbraith, Drolet et al. 2005). Varying incidences have been reported of the presence of oral lesions associated with Crohn's disease (CD) and with ulcerative colitis (UC) (Pitcock, Drumm et al. 2001; Harty, Fleming et al. 2005).

Investigations of OFG include clinical, haematological, radiographic and histopathological examinations to ensure a correct diagnosis. Early diagnosis may lead to prevention of significant cosmetic orofacial problems, and avoid the condition progressing to the development of systemic OFG-related diseases (Mignogna, Fedele et al. 2003).

Debate exists regarding nomenclature and the link between Crohn's disease (CD) and OFG based on the similarities in underlying immunological mechanisms (Satsangi and Jewell 1994; Gibson, Wray et al. 2000; Tilakaratne, Freysdottir et al. 2008). Identification of a relationship between OFG and CD, such as OFG being a precursor to, or an early stage manifestation of CD in a paediatric population, could aid in diagnosis, and to enable early clinical management of the disease. Protocols could be developed to enable greater ability to manage the disease in its infancy and potentially improve short and long term prognosis for both OFG and CD (Bogenrieder, Rogler et al. 2003; Tilakaratne, Freysdottir et al. 2008; Rowland, Fleming et al. 2009).

The null hypothesis for this research is that the incidence and severity of orofacial granulomatosis and other oral involvement do not have a role in paediatric Crohn's disease.

The objectives of each investigation are: -

1. A pilot study to investigate oral manifestations in an Australian paediatric population and cohort sample of South Australian patients
2. A pilot study to establish if there are clinical and histological similarities between OFG and CD in South Australian patients

3. The assessment of the initial management, investigations and management of two paediatric patients presenting with signs and symptoms of OFG

This research is aimed at: -

1. Determining if oral manifestations, including OFG are a precursor to, or an oral manifestation of paediatric CD
2. Establish if the oral manifestations are a separate oral pathological condition.
3. Using the data obtained to develop a visual diagnostic guide for OFG and orofacial manifestations

For diagnosis of OFG and CD thorough investigations involving history taking, clinical assessment and histopathological analysis is required. Through conducting retrospective analysis of data and histopathological specimens, and clinical and serological assessment of paediatric CD patients, greater correlation can be made between orofacial manifestation(s) and CD activity.

Presently a scale for assessing the clinical presentation and severity of OFG and oral manifestations does not exist. Establishment of a visual diagnostic guide will potentially enable greater uniformity and accuracy in diagnosis of the condition by medical practitioners, gastroenterologists and other health care practitioners involved with investigations of OFG and suspected inflammatory bowel diseases.

Ethics approval was obtained from the Human Research Ethics Committee (HREC) from the CYWHS (REC2111/10/11) (See Appendix I).



Chapter II
Literature Review

II. A. OROFACIAL GRANULOMATOSIS

II. A. 1. Definition, Natural History and Prevalence

OFG was defined by Wisenfeld in 1985 to encompass Melkersson Rosenthal syndrome, cheilitis granulomatosa of Miescher, oral sarcoidosis and OCD. Other diseases that may present with chronic facial swelling include hypersensitivity reactions, acquired and hereditary angioedema, Hansen's disease (leprosy), deep fungal infections, Anderson-Fabry disease and Ascher's syndrome (Wiesenfeld, Ferguson et al. 1985) (Fig. 1). OFG describes the clinical syndrome presenting with the swelling of the face, lips or oral tissues in association with histological evidence of noncaseating granulomatous inflammation within these tissues (Leao, Hodgson et al. 2004).

The term 'idiopathic OFG' is reserved for cases that are restricted to the oral region without any identification of a known granulomatous disease. This term should be applied until there has been a diagnosis of a specific granulomatous condition based on systemic manifestations (Tilakaratne, Freysdottir et al. 2008). According to classifications of granulomatous diseases, OFG is considered an immunological aberration as the causative agent or antigenic insult is unrecognized (James 2000; Saalman, Mattsson et al. 2009).

Numerous descriptions of orofacial swellings have been documented through case reports. First described in 1875 by Jonathan Hutchinson, sarcoidosis was defined as a rare multi-system inflammatory disorder of unknown origin characterised histologically by the presence of noncaseating granulomatous disease affecting multiple organs and tissues (Fatahzadeh and Rinaggio 2006). Sarcoidosis is a rare multi-factorial disease and whilst the respiratory system is most commonly affected (90%), chronic cutaneous manifestations occur in around

25% of cases. Manifestations in the orofacial region (10 to 15%) may affect the mucosa, skin, bone and parotid glands (Kolokotronis, Antoniadis et al. 1997; Suresh and Radfar 2005; Fatahzadeh and Rinaggio 2006). There may be asymptomatic ulcerations and swelling of the facial, mucosal and gingival tissues. It has also been associated with rapid alveolar bone loss and increased mobility of teeth (MacFadyen and Ferguson 1996). It most commonly affects individuals in their second to fourth decade of life (Kimani and Aguayo 1998).

In 1928, Melkersson reported orofacial oedema with facial palsy present without a recognized systemic condition. Five years later, Rosenthal noted that lingual fissuring presented with the other two symptoms and proposed naming the condition Melkersson Rosenthal syndrome (MRS) (MacFadyen and Ferguson 1996). The characteristic triad of MRS features comprises of swelling of lips, tongue fissuring and facial paresis (unilateral or bilateral). These features may appear together or at varying intervals to one another (Rogers 1996). Swelling occurs in all patients, but tongue fissuring and facial paresis occur in only 30% of cases (Hodgson, Buchanan et al. 2004).

The term ‘oligosymptomatic MRS’ has been applied to cases in which 1 or 2 features arise. Other features that may present in MRS include gingival hypertrophy, migraines, herpes simplex infection, decreased salivation and lacrimation, involvement of the chin, nose, eyelids and forehead (Wiesenfeld, Ferguson et al. 1985; Mignogna, Fedele et al. 2001; Mignogna, Fedele et al. 2003). Histologically, early lesions show mild epithelial hyperplasia in the dermis, with dilated lymphatics. In the tissue there are also aggregates of histiocytes, lymphocytes and plasma cells. More developed lesions show the characteristic histopathology with multiple small noncaseating granulomas. Throughout the tissue

Langhans giant cells are dispersed (Wiesenfeld, Ferguson et al. 1985; Mignogna, Fedele et al. 2001).

In 1945 Miescher described the presence of cheilitis granulomatosa. He described the repeated presence of chronic or episodic swelling of the labial tissues of one or both lips without facial paralysis (MacFadyen and Ferguson 1996). These symptoms were found to be caused by noncaseating infiltration and obstruction of lymphatic drainage (Sciubba and Said-Al-Naief 2003). CG of Miescher is a rare disorder of unknown aetiology. There may be an increase in the frequency in swelling, resulting in persistent swelling with permanent effects that have minimal response to treatment (Kolokotronis, Antoniadis et al. 1997).

Figure 1. OFG and its relationship to other noncaseating granulomatous conditions-**(Adapted from Boegenrider *et al.* (2003))**

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In 1703, Archibald Pitcairne was the first medical professional to document a report of a condition linking both oral and enteric manifestations. Other descriptions of the occurrence of non-malignant, non-tuberculous forms of enteritis were reported by Morgagni in 1769. He

described the erosive lesions and ulceration of the terminal ileum with involvement of the mesenteric lymph nodes together with a gangrenous appearance to the tissue (MacFadyen and Ferguson 1996).

It was not until 1932 that Burrill Crohn published the first documented detailed description of 'sub-acute or chronic necrotizing and cicatrizing inflammation' of the terminal ileum. Crohn identified that this disease mainly affected young adults, with a male predominance in the proportion of nearly 2:1. He proposed the term "regional ileitis" to differentiate this well-defined clinical entity to other 'benign granuloma(s)' (Crohn 1932). Stained histological specimens obtained by resection, showed varying degrees of acute, subacute and chronic inflammation, with variations in the predominance of polymorphonuclear, round cells, plasma cells and fibroblastic elements (Crohn 1932, Wiesenfeld 1985). In later stages of the disease, the focal areas of inflammation had the appearance of tubercles. These specimens were then differentiated from those present in tuberculosis, and noted to be present throughout the entire alimentary tract (MacFadyen and Ferguson 1996, Crohn 1932).

In a case report published in 1969, Dudeney and Todd established a relationship between the oral and intestinal granulomatous lesions of regional enteritis in a 36 year old male patient (Dudeney and Todd, 1969). They described intestinal symptoms starting 16 years prior, which lead to the diagnosis of CD. In 1968 the patient developed swelling from the left buccal mucosa, which was biopsied and found to be granulomatous tissues without involvement of tuberculosis. Thus they concluded that he had oral Crohn's disease, but found that there had not been any previous literature documenting this presentation (MacFadyen and Ferguson 1996). (Table 1)

Table 1: Summary of conditions with orofacial swelling, their prevalence and year of publication

<i>Condition</i>	<i>Author</i>	<i>Year</i>	<i>Prevalence</i>
Sarcoidosis	J. Hutchinson	1875	1-5/10000*
Melkersson Syndrome	E. Melkersson	1928	n/a
Crohn's Disease	B. Crohn	1932	6-9/10 000 [†]
Melkersson-Rosenthal Syndrome	C. Rosenthal	1933	8/10 000 [‡]
Cheilitis granulomatosa	G. Miescher	1945	8/10 000 [‡]
Oral Crohn's Disease	T. Dudney and I. Todd	1969	41.2% [§]
Orofacial Granulomatosis	D. Wisenfield	1985	n/a

*Orphanet- Orpha number: ORPHA797

[†]Orphanet- Orpha number: ORPHA206

[‡]Orphanet – Orpha number: ORPHA2483

[§]El-Hakim M, 2004

[¶]Harty et al. (2005)

In 1997 Challacombe questioned 'What is the relationship between OFG and current subclinical systemic CD?', 'Is OFG a predictor of the subsequent development of CD?' and 'Is there such a diagnosis of partial MRS or should OFG, OCD and MRS all be considered as part of the same spectrum of disease?' (Challacombe 1997). As yet, there are no published studies or reports which have been able to answer these questions, indicating an area requiring further investigation and research leading to a better understanding of the relationship between OFG and CD.

There is debate within the literature regarding the use of the term OFG in the absence of confirmed CD, and whether the term OFG should be retained following the diagnosis of CD or if the term OCD should be applied (Saalman, Mattsson et al. 2009).

Leao *et al.* (2004) reported that there are few studies examining the gastrointestinal tract of children and adults with OFG. There are published reports of OFG being an initial presentation or a concurrent feature of CD (Bogenrieder, Rogler *et al.* 2003; Leao, Hodgson *et al.* 2004). Ghandour *et al.* (2001) found the number of reported children and adolescents affected by the disease seems to be increasing (Ghandour and Issa 1991). Potential reasons for the lack of investigation into the incidence and prevalence of OFG in any population are that OFG may be under or misdiagnosed since the orofacial clinical manifestation may be misleading (Bogenrieder, Rogler *et al.* 2003). Mignogna *et al.* (2003) also found early recognition of OFG is challenging with a 48% occurrence of atypical onset of OFG, thus believing that this then results in delayed or only suspected diagnosis (Mignogna, Fedele *et al.* 2003).

Currently there is no published data about the incidence and prevalence of OFG in an Australian adult or paediatric population.

II. A. 2. Clinical features

Oral facial granulomatosis (OFG) encompasses a range of clinical symptoms presenting with swelling in the orofacial region. OFG can be multiform, acute, recurrent and/or chronic in nature. It involves atypical sites of the orofacial region such as one or both lips, chin, cheeks, periorbital area, zygomatic tissues, lymph nodes, eyelids and forehead (Wiesenfeld, Ferguson *et al.* 1985; Al Johani, Moles *et al.* 2009). OFG may present with single or multiple minor manifestations unilaterally or bilaterally (Mignogna, Fedele *et al.* 2003). Other clinical features include angular cheilitis, fissuring of the lips (median cheilitis), mucosal swelling, mucosal tags, gingival enlargement (granulomatous gingiva) (Al Johani, Moles *et al.* 2009) and fissuring of the tongue (lingua fissures) (Leao, Hodgson *et al.* 2004; Khouri, Bohane *et*

al. 2005; Grave, McCullough et al. 2009). Neurological manifestations such as facial nerve palsy may occur, facial swelling and erythema and less commonly cervical lymphadenopathy (Leao, Hodgson et al. 2004). (See Table 2).

Table 2. Summary of clinical features of orofacial granulomatosis

<i>Extra Oral Manifestations</i>	<i>Intra Oral Manifestations</i>	<i>Neurological Manifestations</i>
Periorbital swelling	Lingua fissures	Facial palsy
Eyelid swelling	Mucosal tags	
Swelling of the zygomatic region	Cobblestoned mucosa	
Chin swelling	Gingival tags	
Cheilitis granulomatosis	Granulomatous gingiva	
Angular cheilitis	Ulceration	
Cervical lymphadenopathy	Median cheilitis	
Facial erythema		
Lip swelling		
Lip Fissuring		

Cheilitis granulomatosis (CG) is characterized by recurrent or episodic non-tender diffuse swelling of one or both lips (Leao, Hodgson et al. 2004; Grave, McCullough et al. 2009) with no difference in prevalence between the upper and lower lips (Wiesenfeld, Ferguson et al. 1985). This enlargement is generally painless, primarily affecting young adults (Ficarra, Cicchi et al. 1993). Unsightly swelling of the lips and face can be distressing, and can cause children to be self-conscious and withdrawn (Field and Allan 2003). Clinically it can vary from a soft or firm swelling. If it occurs without other clinical signs it is regarded as the

monosymptomatic form of MRS. Episodes of labial enlargement can vary greatly from weeks to months. If severe and persistent, the lips may be permanently enlarged and appear protuberant (Kolokotronis, Antoniadis et al. 1997) (Figure 2a). This results in median cheilitis at the midline of the lips (Figure 2b), and/or angular cheilitis (stomatitis) (Mignogna, Fedele et al. 2001; Leao, Hodgson et al. 2004; Grave, McCullough et al. 2009). The associated perioral skin may be erythematous (Al Johani, Moles et al. 2009), dry and flaky in appearance, although some patients develop a lip-licking habit which can result in artefactual cheilitis and eczema (Leao, Hodgson et al. 2004). In comparison the labial mucosa has an erythematous and granular appearance (Leao, Hodgson et al. 2004; Grave, McCullough et al. 2009).

Figure 2a. Cheilitis granulomatous with crusting of the upper and lower lip with angular cheilitis (Yeung)

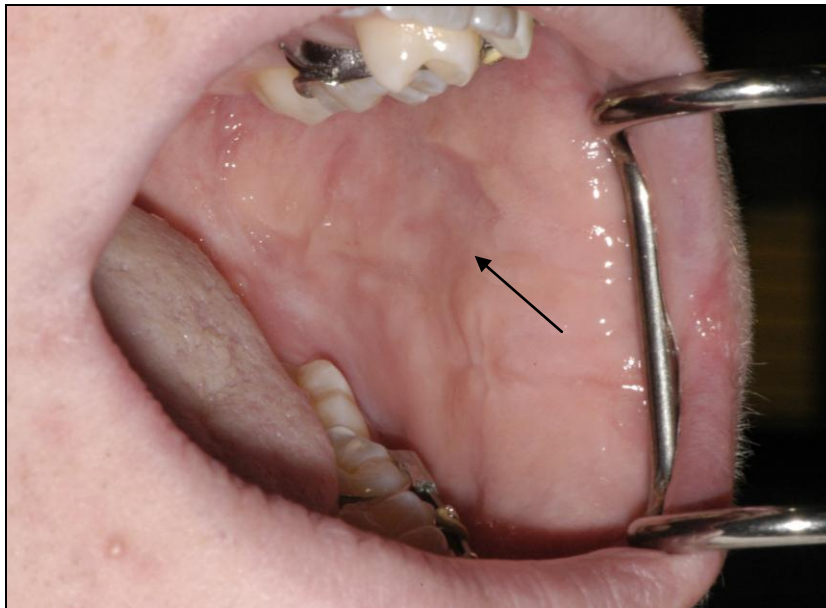


Figure 2b. Cheilitis granulomatous with induration of the upper lip (Yeung)

The most common site for oral ulceration is in the buccal or labial vestibular sulci. Other sites include the anterior, labial or buccal mucosa (Leao, Hodgson et al. 2004) (Figure 3). There are a variety of ulcerations that may occur, with the deeper ulcers having a characteristic well defined erythematous raised border and are linear in nature (Wiesenfeld, Ferguson et al. 1985; Field and Allan 2003). These cause notable discomfort during masticatory function, and predominantly manifest in the buccal and labial vestibular sulci where the hyperplastic tissue folds. The occlusal ridge is also a common site for ulcerations, where the thickened buccal mucosa can become traumatised. These ulcers are often deep, with secondary infections occurring. More superficial ulcerations may occur on any other mucosal surface (Leao, Hodgson et al. 2004). Recurrent aphthous stomatitis (RAS) may also occur in patients with OFG, but are not characteristic for this condition (Field and Allan 2003).

Figure 3. Linear mucosal ulceration (Leao, Hodgson et al. 2004)

Mucosal swelling and gingival enlargement has a variable presentation, ranging from a generalized cobblestoned oral mucosa and full width gingivitis affecting free or attached gingiva (Mignogna, Fedele et al. 2001; Leao, Hodgson et al. 2004) (Figure 4). The ‘cobblestone’ appearance occurs when the buccal and gingival mucosa are swollen to the extent that it forms distinct folds, which may superimpose over normal healthy oral mucosa (Mignogna, Fedele et al. 2001; Leao, Hodgson et al. 2004) (Figure 5). On examination, there is little inflammatory change, absence of bleeding and local aetiological factors commonly associated with gingivitis that is supra and subgingival plaque and/or calculus (Asquith, Thompson et al. 1975; Challacombe 1997; Clayden, Bleys et al. 1997). Affected areas range in colour from normal to salmon pink to red, with a granular appearance (Mignogna, Fedele et al. 2001; Leao, Hodgson et al. 2004; Al Johani, Moles et al. 2009).

Figure 4. Gingival enlargement in OFG (Yeung)**Figure 5. Cobblestoned buccal mucosa (Yeung)**

Another clinical characteristic that may present are pink or red mucosal tags. Often painless manifestations they most commonly arise on the labial or buccal mucosa in the vestibular or retromolar regions (Basu, Asquith et al. 1974; Mignogna, Fedele et al. 2001; Leao, Hodgson et al. 2004) (Figure 6). Tongue fissures may occur, presenting with deep fissures on the

dorsum of the tongue and may be more pronounced on the lateral borders (Leao, Hodgson et al. 2004; Al Johani, Moles et al. 2009) (Figure 7). Fissuring of the tongue is relatively common and occurs within 21.5% to 30.5% (Yarom, Cantony et al. 2004) of the general population. Biopsies from fissured tongue in patients with OFG have not been found to have any histological abnormalities (Wiesenfeld, Ferguson et al. 1985).

Figure 6. Mucosal tag in labial vestibule (Yeung)

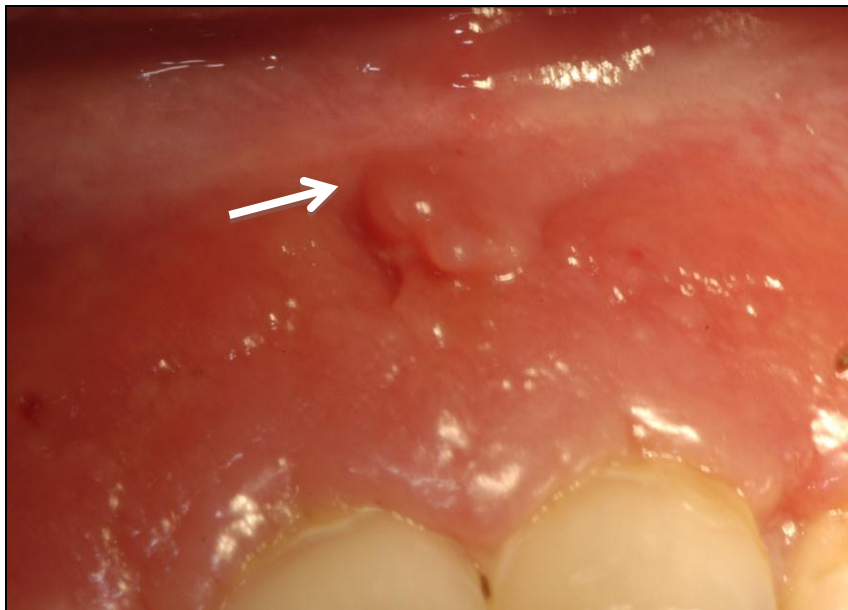


Figure 7. Tongue fissure (Yeung)

Facial swelling may be observed around the perioral or periorbital tissues (Grave, McCullough et al. 2009). These may be persistent and/or recurrent swellings that are soft to palpate, without pitting. The overlying epidermis of the swellings is often erythematous (Leao, Hodgson et al. 2004) (Figure 8). Another rarely occurring symptom in OFG is facial nerve palsy (Bells Palsy). The pathogenesis behind facial nerve palsy is speculative and is either due to direct formation of granulomas along the course of the main stem of the seventh cranial nerve or its sheath (Wiesenfeld, Ferguson et al. 1985; Leao, Hodgson et al. 2004) or compression of the nerve by oedema within the canal in the petrous temporal bone (Wiesenfeld, Ferguson et al. 1985).

Figure 8. Erythematous perioral swelling with diffuse swelling of the lower half of the face (Gue)

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In very severe cases of OFG cervical lymphadenopathy can occur, varying from localized to generalized node involvement. These may or may not be tender to palpate, and vary in consistency and size (Hodgson, Buchanan et al. 2004; Leao, Hodgson et al. 2004).

Presentation of facial swelling was variable according to extent and duration of the swelling. Severe cases feature diffuse swelling of the lower half of the face, compared to mild cases with swelling restricted to one lip or a localized patch of the cheek (Wiesenfeld, Ferguson et al. 1985; Sainsbury, Dodge et al. 1987).

There are few reports of substantial numbers of patients attending a single centre to allow clear descriptions of the early and late clinical features of OFG (Al Johani, Moles et al. 2009). A review of the current literature indicates that there are no published studies on a paediatric population. Al Johani *et al.* (2009) assessed the onset and progression of the clinical manifestations of OFG in an adult population with a follow up period of over 20 years after initial consultation (Al Johani, Moles et al. 2009). The mean age of patients

involved was 32.4 years, and the mean age of onset of OFG was 28.7 years. Analysis of data recorded at the onset of symptoms found five major patterns of disease. These were (1) facial swelling only, (2) facial swelling and other manifestations, (3) oral ulceration only, (4) intra-oral manifestations without facial swelling, and (5) neurological manifestations only (Al Johani, Moles et al. 2009). The most common clinical feature at disease onset was orofacial swelling reported by 53.1% (26/49). Of this group, 57.7% (15/26) had lip swelling only and 42.3% (11/26) had lip swelling and extra and/or intraoral manifestations. Presentation of a single feature at onset included gingival enlargement which was reported in 8.2% (4/49) of cases, and facial nerve palsy in 6.1% (3/49) of patients (Al Johani, Moles et al. 2009).

Analysis of long term results found that 95.9% (47/49) of patients developed facial swelling. Within the category of facial swelling, lip swelling was reported in 98% (46/47) of cases. Of this group, it was observed that both lips were affected in 43.4%, lower lips only 41.5% and upper lip only in 15.2% of patients. Additionally, 49% (24/49) of OFG patients experienced mucosal ulceration over long term assessment period (Al Johani, Moles et al. 2009). This supports results published by Wiesenfeld *et al.* (1985) that CG is the most common clinical presentation followed by oral ulceration (Wiesenfeld, Ferguson et al. 1985).

II. A. 3. Aetiology

A review of paediatric Orofacial granulomatosis (OFG) by Tilakaratne *et al.* (2008) found that as the term OFG encompasses a group of diseases, no specific aetiology or pathogenesis for OFG has been defined (Tilakaratne, Freysdottir et al. 2008). Suggested causative factors of OFG (Grave, McCullough et al. 2009) include foods and preservatives, dental materials, infective agents, immunological agents and genetics (Tilakaratne, Freysdottir et al. 2008). It

has also been observed that approximately 12-60% of affected individuals may have a history of atopy (James and Ferguson 1986; Leao, Hodgson et al. 2004).

Many studies conducted have indicated that OFG may result from hypersensitivity reactions to food and food preservatives (Wray, Rees et al. 2000; Tilakaratne, Freysdottir et al. 2008). Patients with OFG are more likely to develop or exacerbate orofacial swelling when exposed to food additives especially benzoic acid, a commonly used food preservative also found in cosmetics, dyes and plastics. A variety of food products have been identified as causing food hypersensitivity in OFG patients. These products include wheat, dairy products, chocolates (Wray, Rees et al. 2000), eggs, peanuts, cinnamaldehyde, carbone piperitone, cocoa, carvone, carmoisine, sunset yellow dye and monosodium glutamate (MSG) (Sweatman, Tasker et al. 1986; Sciubba and Said-Al-Naief 2003). A common material which may affect OFG patients is tooth paste which contains cinnamaldehyde or carbone piperitone (Sweatman, Tasker et al. 1986).

Whilst literature on dietary causes of OFG is largely limited to case reports, White *et al.* (2006) examined the relationship between patients with OFG and a cinnamon-benzoate free diet (White, Nunes et al. 2006). After 8 weeks on a cinnamon-benzoate free diet, findings included significant improvement in oral and lip inflammatory symptoms. However the improvements were not site specific and it was found that the response to cinnamon-benzoate free diet was greater in individuals with early onset OFG than in those with shorter disease duration (White, Nunes et al. 2006). Benzoate is widely used as a preservative in foods and occurs naturally in many foods such as fruits.

Cinnamon, consisting of cinnamaldehyde, is widely used as flavouring in food, drinks, toothpaste and mouthwashes (White, Nunes et al. 2006; Endo and Rees 2007). At present, the exact role of cinnamon and benzoate in OFG pathogenesis is not clear and it is not known whether these are primary antigens causing disease, an adjuvant or acting via molecular mimicry in sensitized individuals. However, due to the response to a cinnamon-benzoate free diet, White *et al.* (2006) postulated that OFG diagnosed in their study may be the result of a chronic inflammatory process initiated by dietary antigens (White, Nunes et al. 2006).

Further evidence that OFG may be a result of exposure to food additives, a case report by Sweatman *et al.* (1986) investigated the role of carmoisine, sunset yellow and monosodium glutamate. Results indicated that OFG symptoms were episodic, and observed to worsen towards the evening. In addition, symptoms were shown to increase following infection, emotional stress and antibiotic therapy (Sweatman, Tasker et al. 1986). Regression of facial swelling occurred following treatment with a restricted diet. Food colouring, MSG, benzoate preservatives and salicylates were eliminated from the diet. Following a relapse in symptoms, a total elemental diet was introduced with resolution and maintenance of symptoms (White, Nunes et al. 2006).

Dental amalgam, gold, mercury and cobalt have also been reported to cause hypersensitivity reactions in individuals with OFG (Cameron and Middleton 2003; Leao, Hodgson et al. 2004; Endo and Rees 2007; Tilakaratne, Freysdottir et al. 2008). William *et al.* (2007) reported a case of a 10 year old boy with OFG and a history of progressive CG and mucosal ulcerations over a period of 6 months. When patch tested the patient had positive reactions to amalgam and mercury (II) amide chloride (William, Marsch et al. 2007).

There are theories involving microbiological factors in the incidence of OFG (Ivanyi, Kirby et al. 1993). These theories are based on micro-organisms, in particular bacteria that present in chronic granulomatous conditions such as sarcoidosis, tuberculosis and CD (Tilakaratne, Freysdottir et al. 2008). Pathogens that have been studied include *Mycobacterium tuberculosis*, *Mycobacterium paratuberculosis*, *Saccharomyces cerevisiae*, and various types of spirochetes (Ivanyi, Kirby et al. 1993; Riggio, Gibson et al. 1997; Gibson, Wray et al. 2000; Savage, Barnard et al. 2004). Results from studies on *Mycobacterium tuberculosis* and *M. paratuberculosis* in the aetiology of CD and OFG have failed to establish any significant links (Riggio, Gibson et al. 1997). Ivanyi *et al.* (2003) postulated that the presence of serum antibody titres to mycobacterial stress protein in patients with OFG might be of diagnostic value for CD (Ivanyi, Kirby et al. 1993).

If OFG is not caused by allergies or infections, and presents without facial nerve palsy or fissuring it is likely to be related to CD (Dummer, Lurz et al. 1999; Tilakaratne, Freysdottir et al. 2008). Despite oral lesions being uncommon in children, IBD is a common aetiology for persistent oral lesions in the paediatric population (Galbraith, Drolet et al. 2005). Sanderson *et al.* (2005) found that OFG affected individuals with severe oral inflammation were more likely to have intestinal inflammation (Sanderson, Nunes et al. 2005). Field *et al.* (2003) found that 16% of presenting OFG subsequently developed CD (Field and Allan 2003). If intestinal CD commonly develops after the presentation of orofacial symptoms in patients, investigations should be made to determine the average duration between the first presentation of oral signs and symptoms and those of active intestinal CD. This may then lead to the appropriate long-term follow-up protocols being developed to ensure early diagnosis and management of CD if required (Ghandour and Issa 1991).

The role of inflammatory and immunological factors in OFG has been investigated (White, Nunes et al. 2006). Tilakaratne *et al.* (2008) found that although OFG has histopathological features consistent with that of delayed hypersensitivity reactions, the number of studies to investigate this is sparse (Tilakaratne, Freysdottir et al. 2008). Facchetti *et al.* (2000) reported a case investigating the T-cell diversity of both types of lymphocytes in a patient with OFG. They found no significant differences when comparing the T-cell receptor diversity of the lymphocytes accumulating at the site of the lesions with that of peripheral blood lymphocytes. It was concluded that in the OFG patient examined, the majority of T cells have no specificity for a single or for a few antigens and that tissue accumulation of T lymphocytes is the result of a random influx of cells at the site of inflammation (Facchetti, Signorini et al. 2000).

Lim *et al.* (1997) reported that the T cell receptor (TCR) V- β gene use of the T cell infiltrate was associated with the primary lesions seen in patients with OFG (Lim, Stephens et al. 1997). That group showed restricted TCRV- β gene expression by lesional lymphocytes compared with normal peripheral blood lymphocytes (Lim, Stephens et al. 1997) Specific human leukocyte antigen (HLA) genotypes were discovered by Gibson *et al.* (2000). They reported that there are significantly increased levels of HLA alleles in individuals affected with OFG (Gibson, Wray et al. 2000). The results of both studies also suggest that the clinical features of OFG have underlying immunological mechanisms (Gibson, Wray et al. 2000; White, Nunes et al. 2006).

Genetic predisposition was postulated by Meisel-Stosiek *et al.* (1990) based on a study reporting clinical features of OFG patients and their relatives. They found that lingual fissures were seen in 23% of families and recurrent mild facial palsy and facial swelling in

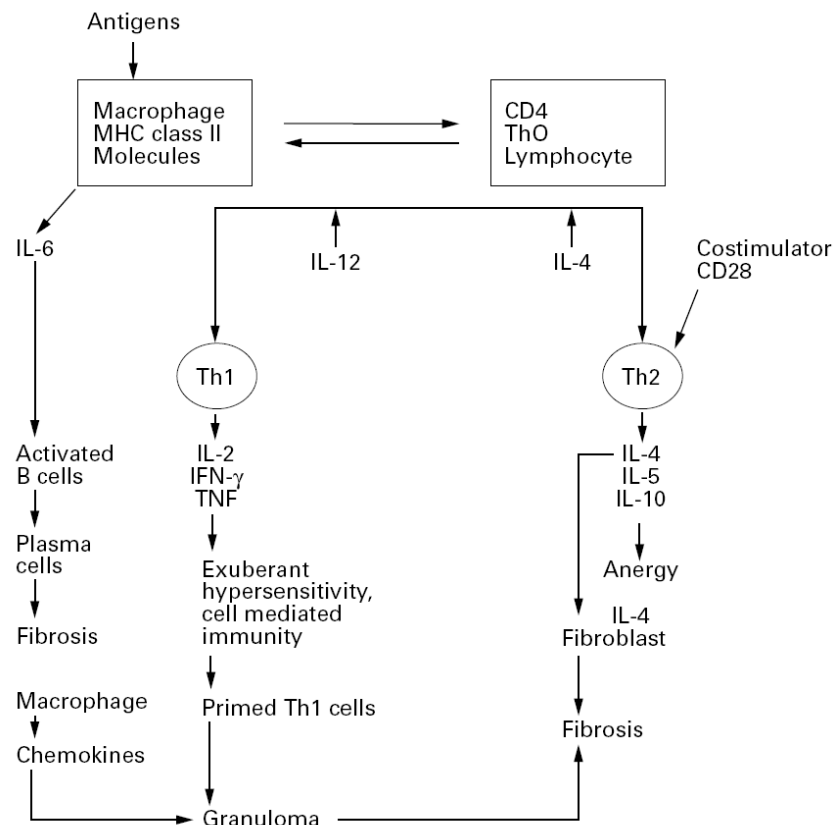
14% of families (Meisel-Stosiek, Hornstein et al. 1990). As fissuring of the tongue occurs within 21.5% to 30.5% (Yarom, Cantony et al. 2004) of the general population, this disputes the earlier postulation about the role of genetics. Campbell *et al.* (2011) found that a family history of inflammatory bowel disease was more likely in CD diagnosed in childhood than in adulthood (Campbell et al., 2011)

II. A. 4. Pathogenesis

The precise pathogenesis of OFG has yet to be explained (Tilakaratne, Freysdottir et al. 2008). The presence and persistence of various agents implicated in the aetiology such as antigens, irritants or other factors result in an active cell mediated hypersensitivity reaction (James 2000; Tilakaratne, Freysdottir et al. 2008). However, the exact antigen inducing the reaction varies in individual patients (Tilakaratne, Freysdottir et al. 2008). As a result of the hypersensitivity reaction, there is formation of a granuloma from the focal compact collection of inflammatory and mononuclear cells (James 2000). This process involves a complex interplay between the causative factor and macrophage activity, T-helper 1 (Th-1) cell response, B cell overactivity, circulating immune complexes and a vast array of biological mediators (Figure 9). Areas of inflammation or immunological reactivity attract monocyte macrophages that may then fuse to form multinucleated giant cells and transform into epithelioid cells (James 2000).

Granulomas may cause lymphatic blockage, resulting in lymphoedema and diffuse swelling of the lips. Tissues with chronic inflammation may produce foci of macrophages and lymphocytes, resulting in noncaseating granulomas within the tissues (Leao, Hodgson et al. 2004).

Figure 9. Complex interplay between initiator and host cellular response resulting in granuloma formation (James 2000)



II. A. 5. Investigations

Due to the varying aetiology, presentation and nature of OFG the clinical, biochemical or histological differentiation is often difficult to determine (Diamond, Patterson et al. 1990).

Debate exists in general surgical and dental literature regarding the extent to which a patient presenting with OFG should be investigated for chronic granulomatous disease elsewhere.

For the best outcome, there should be investigations and management by multi-disciplinary teams including, but not restricted to gastroenterologists, dermatologists, general medical practitioners, dieticians, oral maxillofacial surgeons and dentists (Field and Allan 2003). As

is with any condition, it is important to confirm the diagnosis and identify any causative factors, as well as any associated underlying systemic conditions (Mignogna, Fedele et al. 2003).

It is recommended that thorough investigations of OFG (with and without gastrointestinal symptoms) are necessary to rule out involvement of the GI tract in the disease process. It should involve mandatory gastrointestinal evaluation (Diamond, Patterson et al. 1990; Plauth, Jenss et al. 1991; Galbraith, Drolet et al. 2005). In contrast, Mignogna *et al.* (2001) stated that it is only when the patient has experienced gastro-intestinal signs should other more invasive investigations involving barium studies, endoscopy, and colorectal biopsy be performed (Mignogna, Fedele et al. 2001). Gastrointestinal evaluation involves clinical assessment (Table 3), detailed medical history and haematological and biochemical tests (Mignogna, Fedele et al. 2001). Careful examination of the perianal area is necessary in patients with chronic OFG (Diamond, Patterson et al. 1990). If results fail to substantiate a diagnosis of Crohn's disease, regular follow-up examinations are necessary to detect possible later development of the disorder (Snyder and Cawson 1976; Plauth, Jenss et al. 1991; Galbraith, Drolet et al. 2005). Detailed history taking should also determine whether the patient has experienced weight loss, bowel symptoms, diarrhoea, bloody stool and other systemic symptoms (Galbraith, Drolet et al. 2005; Saalman, Mattsson et al. 2009). If these symptoms have been experienced further procedural investigation is indicated.

Table 3. Possible clinical gastroenterology results of OFG and similar disorders

(Adapted from Leao *et. al.* (2004))

Condition	Gastrointestinal Manifestations
OFG	Normal

CD	Gastrointestinal involvement
Sarcoidosis	Normal
Allergic angioedema	Normal
CG of Miescher	Normal
Cheilitis grandularis	Normal
Exfoliative cheilitis	Normal
Tuberculosis	Normal

Haematological testing involves assessment with a red blood cell (RBC) examination, white blood cell (WBC) count and differential analysis. Suggested Investigations include assessment of the erythrocyte sedimentation rate (ESR), levels of serum electrolytes, serum folate, vitamin B12, C-reactive protein (CRP), iron, transferrin, albumin, immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), immunoglobulin E (IgE), serum angiotensin converting enzyme (SACE), ASCA test (anti-Saccharomyces cerevisiae antibody test) and levels of C1-inhibitor (C1INH) (Mignogna, Fedele et al. 2001; Grave, McCullough et al. 2009; Saalman, Mattsson et al. 2009) (Table 4). Sanderson *et al.* (2005) did not correlate a relationship between any blood parameters and intestinal involvement in a study on OFG patients without gut symptoms (Sanderson, Nunes et al. 2005).

Table 4. Possible haematology and serology results of OFG and similar disorders

(Adapted from Leao *et. al.* (2004))

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Swabs of the affected oral environment can also be taken to enable a diagnosis of bacterial, viral and fungal involvement by simple culture techniques. *Staphylococcus Aureus* (*S. Aureus*) has been identified as a potential cause of oral mucosal inflammation in patients with CD or OFG (Gibson, Wray et al. 2000). Other investigations include nutritional assessment, biopsies, contrast radiography and endoscopy for diagnosis of chronic OFG conditions, and to detect coincidental gastrointestinal involvement (Mignogna, Fedele et al. 2003; Grave, McCullough et al. 2009).

Radiological examination of the small and large intestine and chest is also required to detect any intestinal or respiratory anomalies (Leao, Hodgson et al. 2004) (Table 5). Additionally a tuberculin skin test may be required to rule out tuberculosis (Grave, McCullough et al. 2009). All of these investigations are also necessary to rule out diseases such as sarcoidosis, leprosy, deep fungal infections, Anderson-Fabry disease, Ascher's syndrome, hypersensitivity reactions, acquired and hereditary C1INH-related angioedema, leukemic infiltrate and dentoalveolar abscesses (Khouri, Bohane et al. 2005; Kauzman, Quesnel-Mercier et al. 2006).

Table 5. Possible chest radiography results of OFG and similar disorders (Adapted from Leao *et. al.* (2004))

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In cases with OFG, exclusion of possible systemic diseases and subsequent early diagnosis is generally easy. Diagnosis would be based on the clinical-pathological findings from the investigations performed (Mignogna, Fedele *et al.* 2001; Mignogna, Fedele *et al.* 2003).

Investigations of potential allergens would involve questioning the paediatric patient and their parents on their recent history of atopy, most commonly manifested as allergic rhinitis but also as bronchial asthma, atopic dermatitis, or food allergies (Wray, Rees *et al.* 2000; White, Nunes *et al.* 2006). Plauth *et al.* (1991) found that 60% of individuals with OFG experienced atopy (Plauth, Jenss *et al.* 1991). History taking should include a diet history evaluating details about potential dietary aetiology and materials recently contacted. If indicated, standard and urtcarial patch testing and investigations should be undertaken to determine hypersensitivity reactions to allergens, especially benzoates and cinnamon-related

compounds that are associated with OFG (Wray, Rees et al. 2000; Leao, Hodgson et al. 2004) (Table 6).

Table 6. Possible patch testing results of OFG and similar disorders (Adapted from Leao et. al. (2004))

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Oral Biopsies

Oral sites biopsied are those which are most commonly affected such as the lips, labial and/or buccal mucosa, or gingiva (Field and Allan 2003). Deep biopsies to the muscle layer are essential as granulomas may present in underlying muscle (Mignogna, Fedele et al. 2001; Saalman, Mattsson et al. 2009). There is no published data assessing the method of biopsy, site, or ideal number or size of biopsied specimens required for optimal results. Biopsy specimens may also be stained to determine the presence of acidfast bacilli, fungi and spirochetes, and detect the presence of any foreign bodies (van der Waal, Schulten et al. 2002).

II. A. 6. Diagnosis

Diagnosis of OFG can be made by the clinical presentation of recurrent orofacial swellings (Grave, McCullough et al. 2009) and confirmed by histological findings from investigative OFG biopsies (Leao, Hodgson et al. 2004). Despite the variable presentation of OFG, it can be differentially diagnosed based on clinical presentation (Table 7).

Oral biopsy specimens undergo histopathological assessment involving the use of polarised light microscopy, and haematoxylin and eosin staining (Field and Allan 2003). The histology of 68-100% of OFG biopsy specimens shows noncaseating and epithelioid granulomas with or without multinucleated giant cells (Sanderson, Nunes et al. 2005). Lymphoedema is also a frequent histological finding (Wiesenfeld, Ferguson et al. 1985). Other histological features include oedema, lymphangiectasia, and perivascular lymphocytic infiltration.

Table 7. Differential diagnosis of OFG based on clinical presentation

(Leao, Hodgson et al. 2004)

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Some oral biopsy specimens show the presence of granulomas and some others consist of epithelioid cells and giant cells (Scully, Cochran et al. 1982). Histological changes are not always present or specific, nor are they a prerequisite for establishing the diagnosis (Wiesenfeld, Ferguson et al. 1985; van der Waal, Schulten et al. 2002) (Table 8). Clinical diagnosis of OFG can be established from the patient's history and clinical features alone however a definitive diagnosis is obtained by histological confirmation (Scully, Cochran et al. 1982; Wiesenfeld, Ferguson et al. 1985; van der Waal, Schulten et al. 2002; Leao, Hodgson et al. 2004).

Table 8. Possible histopathology results of OFG and similar disorders (Adapted from Leao et. al. (2004))

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A study by Freysdottir *et al.* (2007) of oral biopsies on patients with OFG analysed the presence of T cells, T cell subsets, B cells, macrophages and cytokines, chemokines, and chemokine receptors in the granulomatous tissues (Freysdottir, Zhang et al. 2007). The result

was that the OFG affected group had raised levels of regulatory T cells, interferon- γ (IFN- γ), interleukin-10 (IL-10) and chemokine ligand 5 (RANTES). Lower levels of macrophages with cluster of differentiation cells (CD68+) were found in the tissues outside the granulomas. Within the granulomas the levels of cluster of differentiation cells on T cells (CD3+ and CD4+) cells and IFN- γ were raised, but levels of interleukin-4 (IL-4) decreased. The conclusive findings of the Th1 environment within the oral tissues resembling that of the observed in gut CD tissues suggests that some OFG patients have both histopathological and immunopathological features resembling those in CD (Freysdottir, Zhang et al. 2007).

II. A. 7. Management

Although Orofacial granulomatosis (OFG) is not life-threatening condition, early detection is important to prevent and cure the unsightly sequelae such as ulcers and facial swelling (Sainsbury, Dodge et al. 1987; White, Nunes et al. 2006; Grave, McCullough et al. 2009). Early detections can sometimes avoid the progression of debilitating systemic manifestations in OFG related diseases such as CD, sarcoidosis, or tuberculosis (Grave, McCullough et al. 2009). Importantly it can enable early identification and management of significant psychological implications on young patients (Sainsbury, Dodge et al. 1987; White, Nunes et al. 2006; Grave, McCullough et al. 2009). Delayed diagnosis resulted in persistent OFG conditions with the longer the duration between onset to treatment time, the less effective treatment was. This lead to unsatisfying clinical improvement and relapses requiring therapy to be repeated (Mignogna, Fedele et al. 2003).

Due to the variable aetiology, chronic nature and potential refractory behaviour of OFG management of the condition is challenging (Sciubba and Said-Al-Naief 2003). The results from treatment of OFG are highly variable and unpredictable regardless of the form the

therapy used. Even with the initial resolution of the presenting OFG, treatment may be followed with periods of remission and exacerbation over months to years (Mignogna, Fedele et al. 2003). Mignogna *et al.* (2003) reported a case of OFG experiencing periods of remission and exacerbation of symptoms with intermittent swelling of the lips with fissures, cobblestones buccal mucosa, bilateral tags of the hard palate (Mignogna, Fedele et al. 2003).

No prospective studies have been published to assess and compare the outcome of different treatment modalities. Presently treatment regimens are empirical and based on the severity of the symptoms with non-surgical treatment most frequently used such as diet therapy, local measures including topical therapy and intralesional therapy and systemic therapy (Sciubba and Said-Al-Naief 2003)

Dietary therapy

Cameron *et al.* (2003) recommended the use of an elemental diet in children and adolescents to avoid corticosteroid use and its potential effects on growth (Cameron and Middleton 2003), however its effectiveness in resolving OFG and sustaining remission of OFG has not been reported in other cases reports. Sweatman *et al.* (1986) reported an adult case with managed by use of an 'elemental diet' consisting of liquid feeds containing proteins as amino acid, carbohydrate as maltodextrins and sugar, fat in small quantities of defined oils, vitamins and minerals (Sweatman, Tasker et al. 1986). This resulted in regression of facial swelling and maintained for 6 months (Sweatman, Tasker et al. 1986). White *et al.* (2006) recommended that for a younger populations with OFG, a cinnamon-benzoate free diet as the primary treatment, with use of topical or systemic therapy as a second option (White, Nunes

et al. 2006). Avoidance therapy had a positive response, with subjective improvement and resolution in 38% of OFG patients (White, Nunes et al. 2006).

Local measures

Topical therapies are considered as the first line of treatment with systemic therapies used when topical treatment has failed to control symptoms (Plauth, Jenss et al. 1991). Topical treatment may yield complete remission in up to 50% of patients (Plauth, Jenss et al. 1991). Topical therapy involves application of a topical steroid preparation alone such as 0.1% triamcinolone acetonide in Orabase, or in combination with antifungal medications. Cases report successful management of mild lip swelling, fissuring, cobblestoned mucosa and angular cheilitis by this therapy (Taylor and Smith 1975; Sciubba and Said-Al-Naief 2003). Improvement of OFG has also been reported following therapy involving topical 0.05% clobetasol propionate cream (Dupuy, Cosnes et al. 1999; Mignogna, Fedele et al. 2003) or with topical 5-aminosalicylate (Dupuy, Cosnes et al. 1999).

Sciubba *et al.* (2003) reported improvement of OFG following topical application of a combination of nystatin, fluocinonide, tetracycline, diphenhydramine and Maalox™ suspension (Sciubba and Said-Al-Naief 2003). Additionally antiseptic and analgesic mouth rinses can be incorporated into the mouth-care regimen when ulcerations are present (Gerson and Triadafilopoulos 2000). Chlorhexidine gluconate 0.2% rinse was found to help maintain gingival architecture (Sciubba and Said-Al-Naief 2003). Field *et al.* (1989) reported successful management of angular cheilitis with topical application of 1% hydrocortisone (Field and Tyldesley 1989).

Casson *et al.* (2000) investigated the role of topical tacrolimus on treatment of oral and perianal CD. Using a low concentration (0.5 mg/g) of tacrolimus for peri oral or perianal administration on 8 children aged 5 to 8 years. It was applied to oral disease in 3 patients, and/or perianal ulcerations in 6 patients with CD. Improvement was seen in 7 out of 8 patients after 6 weeks, with healing within 6 months. No evidence of significant systemic absorption was found, although it was noticed that abrupt cessation and weaning of tacrolimus resulting in rebound worsening of the signs and symptoms (Casson, Eltumi *et al.* 2000).

Intralesional therapy

Sciubba *et al.* 2003 reported that patients managed with intralesional triamcinolone injections responded well (Sciubba and Said-Al-Naief 2003). Therapy with injection of high concentrations of delayed-release triamcinolone acetonide (0.1%) was found to be most effective on moderate to severe and persistent facial and CG (Mignogna, Fedele *et al.* 2003; Mignogna, Fortuna *et al.* 2008). Repeated intralesional injections have been reported with dosage modification due to recurrent episodes of lip swelling and formation of tissue tags at different oral sites (Sciubba and Said-Al-Naief 2003; Leao, Hodgson *et al.* 2004). Problems associated with this form of therapy were due to pain on application (Field and Tyldesley 1989) resulting in limitations to the volume of triamcinalone injected, especially in paediatric patients (Grave, McCullough *et al.* 2009). In some cases bilateral anaesthesia to the region was required or managed with use of topical anaesthetic gel (Mignogna, Fortuna *et al.* 2008). There are presently no published reports on the long term outcome of intralesional corticosteroid therapy.

Systemic therapy

When there are significant orofacial clinical signs and symptoms, systemic pharmacology has been used for management of OFG. Mignogna *et al.* (2003) reported partial to complete resolution of zygomatic and periorbital swelling following management with short-term systemic oral prednisolone (Mignogna, Fedele *et al.* 2003). Short term systemic oral steroids were also found to have a great effect for severe cases over a short term period (Wiesenfeld, Ferguson *et al.* 1985; Stricker, Braegger *et al.* 2001) such as painful ulcerated buccal lesions, but not as successful at permanently reducing facial or labial oedema (Ghandour and Issa 1991). Field *et al.* (2003) recommended that care should be taken when using systemic steroids in paediatric patients as the dosage and course of treatment will have long term effects on growth and development, immune suppressive mechanisms, anti-inflammatory and adrenal insufficiency effects. Additionally there may be inhibition of the body's natural reparative effects, as well as the manifestation other Cushingoid symptoms (Field and Allan 2003).

Following initial OFG treatment with steroids, upon withdrawal and tapering of the steroid dose there was a tendency for recurrence and relapses of oral symptoms (Ficarra, Cicchi *et al.* 1993; Galbraith, Drolet *et al.* 2005). Galbraith *et al.* (2005) found that as a result, repeat courses of steroids were required with long term successful outcome achieved with use of varying combined therapies involving azathioprine and sulfasalazine (Galbraith, Drolet *et al.* 2005). Dummer *et al.* (1999) and Bogenrider (2003) both reported cases managed with initial treatment involving oral methylprednisolone and mesalamine. Following the initial course, the steroid dose was tapered resulting in a relapse of symptoms. This was managed by introduction of oral metronidazole which allowed for further tapering of the steroid dose with

successful improvement (Bogenrieder, Rogler et al. 2003) and resolution of symptoms (Dummer, Lurz et al. 1999). William *et al.* (2007) reported successful resolution and management of OFG with treatment involving 5-aminosalicylic acid derivative and oral prednisolone (William, Marsch et al. 2007).

Other oral medications that have been used in combination with steroid therapy include azathioprine, clofazimine, hydroxychloroquine, danazol, cyclosporine, sulphasalazine, thalidomide, tacrolimus and antimicrobials (Dupuy, Cosnes et al. 1999). Diamond *et al.* (1990) reported slow progress but successful management of OFG following treatment with sulphasalazine and metronidazole (Diamond, Patterson et al. 1990). Similar slow progressing outcomes were reported by Clayden *et al.* (1997) following initial therapy with systemic corticosteroids, which were replaced with sulphasalazine (Clayden, Bleys et al. 1997). As *Staphylococcus aureus* is a potential cause of oral mucosal inflammation in patients with CD or OFG, use of anti-staphylococcal medication (antibiotics) results in a rapid response to treatment (Gibson, Wray et al. 2000).

Thalidomide (an inhibitor of TNF alpha synthesis) has been reported to be successful in OFG/OCD management. Hegarty *et al.* (2003) reported 5 cases with effective thalidomide management of CD and OCD as a short-term treatment option in appropriately counselled patients. Therapy involved low-dose thalidomide (50mg daily) for cases of OFG/OCD that were non responsive to recognized immunosuppressant therapy (Hegarty, Hodgson et al. 2003).

Surgical therapy

Surgical reduction of facial swelling is generally not warranted or found to be reliably effective (Worsaae, Christensen et al. 1982). However, in severely disfiguring cases surgical intervention may be indicated (van der Waal, Schulten et al. 2002; van de Scheur, van der Waal et al. 2003). Cheiloplasty can be provided on only severely disfiguring cheilitis once it has been brought into a quiescent phase. Post-operatively, surgical patients were treated with biweekly to monthly triamcinolone 0.1% injections for 2-6 months to prevent relapse. A reported result by van der Waal *et al.* (2002) was that the combined therapies were moderately effective, although minor recurrent episodes of lips swelling still occurred (van der Waal, Schulten et al. 2002).

II. B. INFLAMMATORY BOWEL DISEASE

II. B. 1. Definition and Epidemiology

Inflammatory bowel disease (IBD) is the term given for a group of disorders characterised by chronic intestinal inflammation of unknown aetiology. IBD is common in industrialised countries, and is not age restricted, however 30% of cases appear in children. Early onset IBD however may have a high familial link, and is primarily characterized by colonic involvement. (Ravikumara and Sandhu 2006).

Crohn's disease (CD) and ulcerative colitis (UC) are the two main disorders that make up IBD (Rowe 2009). Both diseases are chronic and currently have no cure (Valusek. P 2010), with the disease alternating between bouts of remission and inflammatory states (Valusek. P 2010; Wu. G 2010) that have a significant impact upon patient quality of life (Wilcox, Dragnev et al.).

In 1932 Burill Crohn first described CD as a transmural process producing focal ulcerations throughout the gastrointestinal tract (Crohn, Ginzburg et al. 1984). It most commonly involves the terminal ileum, but also presents at any point of the alimentary canal from the mouth to the anus (Ravikumara and Sandhu 2006). Characteristic presentations include abdominal pain and diarrhoea, which may be complicated by fistulisation and/or obstruction (Wu. G 2010).

The incidence and prevalence of CD varies with geographic location (Wu. G 2010).

Comparability of epidemiological studies should take into account the disease classification system used, as there are varying categories i.e. different 'age of diagnosis' categories given in the Vienna (1998) and Montreal (2005) classification criteria. In an adult population, CD incidence rates in Canada are 20.1 cases per 100 000 population (Lowe, Roy et al. 2009). This rate is far greater than those described for the European literature, with various studies reporting ranges from 0.7 to 9.8 cases per 100,000 persons (Wu. G 2010). In an Asian population the prevalence ranges from 0.5 to 4.2 per 100,000 (Wu. G 2010). The lowest recorded rates of new cases appear to be in South Africa (0.3-2.6 per 100,000) and Latin America (0-0.03 per 100,000) respectively (Kornbluth 1998; Panes, Gomollon et al. 2007). It is unknown whether this is related to low diagnosis or low prevalence.

The incidence and the prevalence of CD (especially colonic CD) has increased over the last 5 decades (Auvin, Molinie et al. 2005), predominantly in the Northern Hemisphere. Panes (2007) described a higher incidence of IBD in urban areas, whilst Nikolaus (2007) found that prevalence was higher in the more affluent demographic. However these results may merely be due to difficulties in diagnosis in rural and low affluence situations (Panes, Gomollon et

al. 2007). In adults, genetic and environmental risk factors are evident (Nikolaus and Schreiber 2007). These include Hebrew and American First Nation ancestry, as well as a history of five or more reportable enteric diseases (Lowe, Roy et al. 2009).

Over 80% of CD cases are diagnosed before the age of 40 years (Freeman 2004), with a mean age of diagnoses described as being 32 years of age (Magro, Portela et al. 2009) to 38.7 years of age (Lowe, Roy et al. 2009). In other studies, it has been recognized that the female to male case ratio varies with age with women having an increased risk that increases with age (Wu, G 2010).

It has been documented that over the past 10 years there has been an increasing frequency of incidence of CD in the paediatric population aged sixteen years or less (Phavichitr, Cameron et al. 2003)ESPGHAN (2005), with 20-30% of CD patients being diagnosed before twenty years of age (Phavichitr, Cameron et al. 2003). Retrospective and prospective studies from Europe, Australia and the United States show increased incidence in rates of 0.1 to 4.6 (in the year 2003) over a thirty year period (ESPGHAN, 2005) (Table 9).

Table 9. Incidence of CD in children and adolescents per 100,000 children per year.

(Adapted from ESPGHAN (2005))

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The only published Australian data involving children with an IBD in Australia was a retrospective study by Phavichitr *et al.* (2003). It involved data collected over a thirty-one year period of children under the age of 16 years old initially diagnosed with CD at the Royal Children's Hospital in Melbourne, Australia. The incidence of CD increased from 0.128 to 2.0/100 000, with a disproportionate over-representation of children from urban backgrounds (Phavichitr, Cameron *et al.* 2003). However, no correlation or investigation was made between the incidence and prevalence of OFG and the IBD in this study, resulting in an

unknown relationship between OFG and IBD in an Australian paediatric cohort (Phavichitr, Cameron et al. 2003).

In a paediatric population diagnosed with CD the mean age of diagnosis has been found to be 10.1 (Pfefferkorn, Burke et al. 2009) to 10.3 (Heyman, Kirschner et al. 2005) years of age. In a paediatric population, there is a greater incidence of CD in males, described as being 54% (Heyman, Kirschner et al. 2005) to 65 % (Pfefferkorn, Burke et al. 2009). Lowe *et al.* (2009) found a female/male ratio among incidence cases was 0.74 for the 0-14 year-old group, 1.30 for the 15-64 year-old group, and 1.77 for the cases older than 65 years-old (Lowe, Roy et al. 2009). Sauer *et al.* (2009) also found male predominance in paediatric CD (Sauer and Kugathasan 2009) (Table 10).

Table 10. Male preponderance in paediatric CD compared to adult CD (Source: Sauer 2010)

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II. B. 2. Classification and Disease Activity Index

The characterization and classification of IBD is currently based upon the *Montreal Classification* of 2005. This classification system is based upon the clinical presentation of the disease based upon the first point of diagnosis (A), location of inflammation (L) and the presentation of the disease (B) (Gasche, Scholmerich et al. 2000). Age is a defining characteristic of CD as it often presents in a much younger population (aged sixteen and below) than other colonic diseases (Silverberg 2005). By having a widely accepted sub-classification system recognised and used, it was intended to provide a basis for future research (Gasche, Scholmerich et al. 2000) (Table 11).

Table 11. Summary of revised ‘Montreal classification’ of Crohn’s disease (Gasche, Scholmerich et al. 2000)

Age at diagnosis (A)			
A1	16 years or younger		
A2	17–40 years		
A3	Over 40 years		
Location (L)	Upper GI modifier (L4)		
L1	Terminal ileum	L1 + L4	Terminal ileum + Upper GI
L2	Colon	L2 + L4	Colon + Upper GI
L3	Ileocolon	L3 + L4	Ileocolon + Upper GI
L4	Upper GI	–	–
Behaviour (B)	Perianal disease modifier (p)		
B1*	Nonstricturing, nonpenetrating	B1p	Nonstricturing, nonpenetrating + perianal
B2	Stricturing	B2p	Stricturing + perianal
B3	Penetrating	B3p	Penetrating + perianal

**B1 category should be considered ‘interim’ until a prespecified time has elapsed from the time of diagnosis. Such a time period may vary from study to study (eg, 5-10 years is suggested) but should be defined in order for B1 behaviour to be considered ‘definitive’. GI Gastrointestinal*

Location differentiates CD from other GI conditions as inflammation is most prevalent and severe in the ileum, ileo-colon and colon (Gasche, Scholmerich et al. 2000).

Classification of IBD disease behaviour is recognised as being problematic, as the disease categories are not necessarily independent (Gasche, Scholmerich et al. 2000). There are also a number of factors that may lead the inter-observer to disagree in the assignment of disease behaviour. As various disease behaviours can coexist, it is difficult to determine which behaviour is the 'primary' feature. Another problem is that disease behaviour has been shown to change or progress over the course of the disease in some patients..

Disease Activity Index

The Paediatric Crohn's Disease Activity Index (PCDAI) (Figure 10) is a validated measure of disease activity comprised of historical, laboratory and physical examination parameters (Shepanski, Markowitz et al. 2004). This multi-item measure includes assessment of linear growth and less emphasis on subjectively reported symptoms and is therefore more sensitive than the adult-derived Crohn's Disease Activity Index (CDAI) (Otley, Loonen et al. 1999).

An abbreviated PCDAI was proposed which removes the need for laboratory evaluations of calculated height velocity. Shepanski *et al.* (2004) found that there was no significant difference in the sensitivity of the tests and their ability to predict disease activity (Shepanski, Markowitz et al. 2004).

A multicentre study by Hyams *et al.* (2005) found that the PCDAI was sensitive to changes of disease state during treatment. It was concluded that the index was therefore useful to evaluate interventional trials in paediatric patients (Hyams, Markowitz et al. 2005).

Figure 10. Paediatric Crohn's Disease Activity Index

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II. B. 3. Crohn's Disease Characteristics

CD is a chronic illness with significant impacts on health-related quality of life (Wilcox, Dragnev et al.). If untreated, clinical signs and symptoms of CD may result in significant intra and extra-intestinal manifestations that have significant impacts on daily quality of life, and general growth and developmental impairments (Crohn, Ginzburg et al. 1984; Sathiyasekaran and Shivbalan 2006). CD is a life-long disorder and may appear at any time from early childhood to late adulthood (Freeman 2004). Symptoms may have been present for variable periods of time, from months to years prior to establishment of a diagnosis (Freeman 2004). With the occurrence of a single or multiple events (i.e. an infectious agent), this may generate an insidious inflammatory cascade causing clinical symptoms and a common end-pathological change diagnosed as CD (Freeman 2004).

The phenotypical expression of CD is age-onset dependent, reflecting on the dynamic nature of the disease. Children and adolescents experience a more severe, extensive and complicated disease than most adults and the elderly (Freeman 2004). Thus early and late onset CD is increasingly recognized as distinct entities that can be differentiated not only in regard to their natural history, but also to the underlying mechanism of inflammation and response to therapy (Van Limbergen, Russell et al. 2008). Long term evaluation has found that the disease is progressive, and may have intermittent activity with some experiencing prolonged periods of sub-clinical disease and others expressing a complex disease with stricture formation and penetrating complications (Freeman 2004).

Paediatric-onset Crohn's DiseaseGastro-intestinal Characteristics

CD may potentially involve any site from the mouth to anus, with a predilection for the distal small intestine and proximal colon in children (Freeman 2007; Freeman 2009). CD can occur in the upper GI tract, usually with disease elsewhere in the ileum, colon or both. Upper GI involvement may rarely occur independently of lower GI involvement (Freeman 2009). In a paediatric population there is a higher frequency of upper GI involvement comparative to adult and elderly onset CD (Freeman 2009).

Van Limbergen *et al.* (2008) found that at the time of diagnosis in children, 51% had CD involving the small bowel and colon (L3), colon (L2) in 36%, and ileum (L1) in 6%, and the upper GIT was affected in 51% of cases. They also observed greater colonic involvement in younger onset CD (Van Limbergen, Russell *et al.* 2008). Similar findings were reported by Vernier Massouille *et al.* (2008) with the most frequent CD location at diagnosis and maximal follow-up was the terminal ileum/colon (L3). Overall, 36% (102/281) of children had upper GI involvement (L4) at diagnosis (Vernier-Massouille, Balde *et al.* 2008). Sauer *et al.* (2010) reported that up to 80 to 90% of children with CD experienced colonic disease, compared to approximately 50% of adults with colonic CD (Table 12) (Sauer and Kugathasan 2009).

Table 12. Higher ileocolonic disease prevalence in paediatric CD compared to adult CD**(Sauer and Kugathasan 2009)**

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CD developing in children and adolescents tends to be more severe, resulting in significant disease complication including other complications including intestinal haemorrhage, obstruction, perforation, abscess' and/or fistula formation (Walker-Smith 1994; Singh, Mc et al. 2004; Sathiyasekaran and Shivbalan 2006; Freeman 2009).

Vernie Massouille *et al.* (2008) assessed a paediatric population and found that 29% of children with CD were found to have complicated disease defined as perforating and/or structuring disease at diagnosis (Vernier-Massouille, Balde et al. 2008). They also found that the behaviour of CD was observed to have a dramatic change over a follow-up period of 7 years. Results showed that CD generally evolved from non-penetrating, non-stricturing disease (B1) to stricturing (B2) or penetrating (B3) disease. The proportion of patients who evolved from B1 to B2 was 32%; from B1 to B3, 11%; and from B2 to B3, 16%. Thus, B2

and B3 phenotypes increased from 25% to 44% and 4% to 15%, respectively, whereas B1 phenotypes decreased from 71% to 41% between diagnosis and last follow-up (Vernier-Massouille, Balde et al. 2008) (Table 13).

Table 13. CD phenotype demonstrates progression of disease from inflammatory to structuring and penetrating disease (Sauer and Kugathasan 2009)

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Depending on the site of involvement of the GI tract there may be abdominal pain and systemic symptoms (Walker-Smith 1994; Faubion and Bousvaros 2006; Sathiyasekaran and Shivbalan 2006). On first presentation of only dyspeptic-type epigastric pain or unexpected ileal inflammatory process appendicitis may be suspected (Freeman 2009). The presentation of abdominal pain, diarrhoea and weight loss often lead to specialist referral (Freeman 2009). This characteristic triad of symptoms may not be universally present, and only a single symptom may present (Freeman 2009). Diarrhoea also occurs in two thirds of affected children, with constipation rarely a concern, and gross blood in the stool is an unusual presentation (Walker-Smith 1994).

Extra-intestinal Manifestations

Other extra-intestinal manifestations (EIMs) include perianal disease. Perianal disease may present with abscess formation, perirectal and perianal fistulisation, and may precede

intestinal manifestation by years (Singh, Mc et al. 2004). Vernie Massouille *et al.* (2008) found that 9% of paediatric patients had perianal disease (abscesses or fistulae) at diagnosis and 27% when followed up 7 years later (Vernier-Massouille, Balde et al. 2008).

Fifty percent of affected individuals may experience fever, but there may also be fatigue, anorexia, weight loss and diminution of growth velocity in affected children (Ulnick and Perkins 2001). Extra-intestinal findings may present without significant intestinal symptoms (Freeman 2004) and may manifest in 25-30% of CD patients (Ulnick and Perkins 2001). These include skin manifestations including erythema nodosum, and pyoderma gangrenosum (Tonkovic-Capin, Galbraith et al. 2006). There may be orofacial signs and symptoms, ocular manifestations, as well as arthritis, liver and renal manifestations (Ploysangam, Heubi et al. 1997; Tonkovic-Capin, Galbraith et al. 2006).

Weight loss is seen in fifty percent of children with CD, with failure to thrive (Phavichitr, Cameron et al. 2003). Malnutrition occurs as a result of suboptimal dietary intake, increased GI losses, malabsorption, delayed gastric emptying and increased requirements associated with marked inflammatory activity (Phavichitr, Cameron et al. 2003; Heyman, Kirschner et al. 2005). Severe mucosal inflammation leads to the loss of cellular constituents and hematochezia and results in protein-losing enteropathy, iron-deficiency anaemia, vitamin deficiencies, increased faecal loss of calcium, zinc and magnesium (Ulnick and Perkins 2001; Phavichitr, Cameron et al. 2003; Heyman, Kirschner et al. 2005; Sathiyasekaran and Shivbalan 2006).

Growth failure with decreased growth velocity often precedes GI symptoms. Absolute height deficiency may present in 30% at the time of diagnosis (Phavichitr, Cameron et al. 2003).

Permanent growth failure can occur as a result of chronic under nutrition, administration of corticosteroids, low levels of insulin-like growth factor (IGF-1) and alteration of cytokine profiles (Ulnick and Perkins 2001; Phavichitr, Cameron et al. 2003). There may also be a delay in sexual maturation, which can be related to decreased self-esteem and socialization problems (Ulnick and Perkins 2001). There may even be irreversible loss of growth potential in those who reached puberty prior to having CD (Ulnick and Perkins 2001). If diagnosed and remission is obtained before puberty, there are greater chances for CD affected children to draw near the mean growth and height velocity for their age (Ulnick and Perkins 2001).

Bone disease is a common occurrence in CD affected paediatric patients as it is caused by malnutrition, or by the various effects of cytokines and glucocorticoid therapy taken for treatment and control of the disease. With effects on growing and developing bones, there is potential for osteoporosis to develop (Ulnick and Perkins 2001; Cameron and Middleton 2003).

Oral Characteristics

Clinical oral signs and symptoms in patients diagnosed with CD are referred to as oral Crohn's disease (OCD). In children there is a higher expression of the initial manifestation of CD by oral lesions which may occur years ahead of intestinal symptoms (Khouri, Bohane et al. 2005). Not all clinical features of OCD are present in every patient, with a wide range in individual variations in the signs and symptoms that present (Ghandour and Issa 1991; Dummer, Lurz et al. 1999). It has been reported that the onset of oral symptoms occurs at a younger age (Dupuy, Cosnes et al. 1999). Onset of oral lesions may precede (Plauth, Jenss et al. 1991) or establish at any time during the intestinal disease (Basu and Asquith 1980; Scully, Cochran et al. 1982; Harty, Fleming et al. 2005). Pittock *et al.* (2001) also found that

children with OCD at the time of examination were more likely to have macroscopic and microscopic disease proximally in the GI tract. Those with OCD had a shorter duration of systemic symptoms before presentation, but this did not reflect on the severity of oral symptoms (Pittock, Drumm et al. 2001).

Mignogna *et al.* (2001) also reported that OCD they may precede intestinal symptoms by several years (Mignogna, Fedele et al. 2001). They have also occurred before the diagnosis of intestinal CD in 35% of cases in which bowel symptoms were only evident months after the incidence of OFG (Ghandour and Issa 1991; Dummer, Lurz et al. 1999). There are reports of OFG presenting and being diagnosed between 6 to 9 years of age, and comparatively earlier than the diagnosis of CD in children (Plauth, Jenss et al. 1991; Dupuy, Cosnes et al. 1999).

It has been found that there is a greater incidence of OCD in males at a young age of onset (Walker-Smith 1994). Walker-Smith found 80% of paediatric patients with CD and 41% of children for UC had oral lesions (Walker-Smith 1994; Galbraith, Drolet et al. 2005).

Oral CD is associated with a high prevalence of anal involvement, and only one third of CD paediatric patients were found to develop anal symptoms (Dupuy, Cosnes et al. 1999).

Additionally, there have been reports of CD where there were only oral and anal lesions reported. In paediatric CD, there is also a high frequency of oesophageal involvement, and a high prevalence of oesophageal and anal localizations (Eisenbud, Katzka et al. 1972; Ulnick and Perkins 2001). Other studies indicate a high prevalence of oral CD associated with oesophageal and anal manifestations (Dupuy, Cosnes et al. 1999).

Oral localisation of CD also raises questions about the role of environmental factors i.e. toothpaste, and foods (Dupuy, Cosnes et al. 1999), however further research is required.

Adult-onset Crohn's Disease

Gastro-intestinal Characteristics

It has been reported that with the increasing age of onset of CD, there is gradually decreasing colonic involvement with increase in ileal involvement (Van Limbergen, Russell et al. 2008) (Table 14). Presenting symptoms of CD include a low-grade fever, course of diarrhoea, abdominal pain, weight loss and general fatigue (Wu. G 2010).

Table 14. Differences in Phenotypic and Natural History Characteristics of Paediatric- and Adult-Onset IBD (Kugathasan, Baldassano et al. 2008)

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Extra-intestinal Characteristics

In adults EIMs affect up to 30% of patients (Caprilli, Angelucci et al. 2005). Caprilli *et al.* (2005) reported that the occurrence of on EIM seems to predispose the patient to others that may be related to CD or unrelated to the disease. EIM forms include perianal involvement with skin tags, fistulae, abscesses and scarring (Wu. G 2010). Reported skin manifestations include erythema nodosum and pyoderma gangreosum (Nikolaus and Schreiber 2007). Eye involvement in CD included lacrimal obstruction, uveitis or episcleritis (Manganelli, Turco et

al. 2009). Joints may also be affected with peripheral and/or axial arthritis (Nikolaus and Schreiber 2007). Other EIM includes spondylarthropathy and primary sclerosing cholangitis (PSC) (Caprilli, Angelucci et al. 2005). Metabolic bone disease such as osteoporosis and osteopenia affects 20 to 50% (Caprilli, Angelucci et al. 2005) of both male and female adults with CD.

Oral Crohn's Disease

There are varying reports on the prevalence of OCD in an adult population, ranging from 0-9% (Dupuy, Cosnes et al. 1999), 5-20% (Ploysangam, Heubi et al. 1997; Dummer, Lurz et al. 1999) to 10-37% (Mignogna, Fedele et al. 2001). Correlation has been made between the incidence of oral CD and the activity of CD in an adult population (Ghandour and Issa 1991; Plauth, Jenss et al. 1991; Dummer, Lurz et al. 1999). Symptoms are the same as that reported in paediatric-onset OCD.

II. B. 4. Aetiology and Pathogenesis

The exact aetiology and pathogenesis of CD remains unknown (Asakura, Suzuki et al. 2008) but current theories implicate the role of genetic, immunologic, microbial, environmental, dietary and psychosocial factors as potential causative agents (Grossman and Baldassano 2008; Grossman. A 2009; Wu. G 2010). It is suggested that CD is multi-factorial with an interaction between predisposing genetic, environmental and host factors, and a triggering event is necessary for the disease to develop (Grossman. A 2009).

Genetic and Immunological Factors

There is evidence that there is an inheritable risk for the development of CD. It is thought that most of the genes involved in the development of the disease play a role in mucosal immunity

and are found on the mucosal barrier epithelium (Thoreson and Cullen 2007). Parkes *et al.* (2007) found that genetic evidence strongly implicated defects in the early immune response, particularly innate immune pathways and the handling of intracellular bacteria in the pathogenesis of CD (Parkes, Barrett et al. 2007).

A high rate of CD between monozygotic twins (44.4%) compared with dizygotic twins (3.8%) was reported in a Swedish study of an unselected twin registry (Halfvarson, Bodin et al. 2003). This study found that the genetic component is necessary but not sufficient for causing CD, thus supporting the multifactorial nature of CD (Halfvarson, Bodin et al. 2003). About 30% of patients with CD diagnosed prior to 20 years of age were found to have a positive family history. The percentage decreases to 18% for patients whose disease is diagnosed at age 20-39 years and to 13% after age 40 years (Wu. G 2010).

Genetic assessment has been conducted by genome-wide associated scanning (GWAS) employing high-density single nucleotide polymorphism (SNP) array technology was increased the identification of possible genetic factors linked to CD (Sauer and Kugathasan 2009). It has enabled identification of variants in innate immunity genes, particularly those mediating autophagy and bacterial sensing. Several genes are thought to increase susceptibility to CD such as ATG16L1, IRGM and NOD2 (Coulombe and Behr 2009; Sauer and Kugathasan 2009).

Mutations for CD were first found on the *NOD2/CARD15* gene on chromosome 16. The gene regulates intracellular immune response to bacterial products. It is recognized that mutations with this gene result in phenotypic characteristics such as stricturing disease, ileal involvement, and younger age at diagnosis (Grossman. A 2009).

IRGM and ATG16L1 gene mutations are associated with the phenotypic characteristic of specific ileal involvement. It is recognized that both genes are involved in autophagocytosis, an essential component of the innate immune response targeted towards pathogen-derived proteins (Parkes, Barrett et al. 2007; Grossman. A 2009). Additionally, mutations localised to an area on chromosome 5q for the IBD-5 gene has been identified as being present in CD (Thoreson and Cullen 2007).

It is acknowledged that a majority of genetics analysis has been done in adult cohorts with adult-onset disease, with less known about early-onset variants (Sauer and Kugathasan 2009). Sauer and Kugathasan (2009) hypothesize that paediatric-onset IBD is more likely to be influenced by genetics compared with late or adult-onset IBD, as there is less time for environmental modifiers to have influenced the disease. Studies in paediatric CD involving GWAS have demonstrated that autophagy genes play a role (Peterson, Guthery et al. 2008; Scherr, Essers et al. 2009).

Kugathasan (2008) found 2 risk variants not previously reported in adults. Using more than 1000 cases of paediatric IBC, 2 novel loci, the TNFRSF6B and PSMG1 genes were identified. The TNFRSF6B gene encodes for a receptor that was found to increase the risk for paediatric-onset CD (Kugathasan, Baldassano et al. 2008). However, it has been recognized that that further GWAS studies on an exclusively paediatric-onset CD cohort is required to identify if there are any additional susceptibility genes (Sauer and Kugathasan 2009).

Segal *et al.* (1976) first investigated the role of immune deficiency in CD. In studied in-vivo and in-vitro using *Escherichia coli* in patients with CD, they found that reduced concentrations of pro-inflammatory cytokines during the acute phase of bacterial infection lead to defective removal of the bacteria. This in term resulted in a secondary chronic inflammatory inflammation (Segal and Loewi 1976; Coulombe and Behr 2009). This theory was further discussed by Casanova and Abel (2009) who suggested that CD may be caused by inborn errors of macrophages, resulting in impaired attraction of granulocytes to the gut wall. This would result in the impaired clearance of intruding bacteria thus precipitating the formation of granulomas (Casanova and Abel 2009) (Figure 11).

Figure 11. Model of intestinal chronic inflammation caused by errors of macrophages in patients with CD (Casanova and Abel 2009)

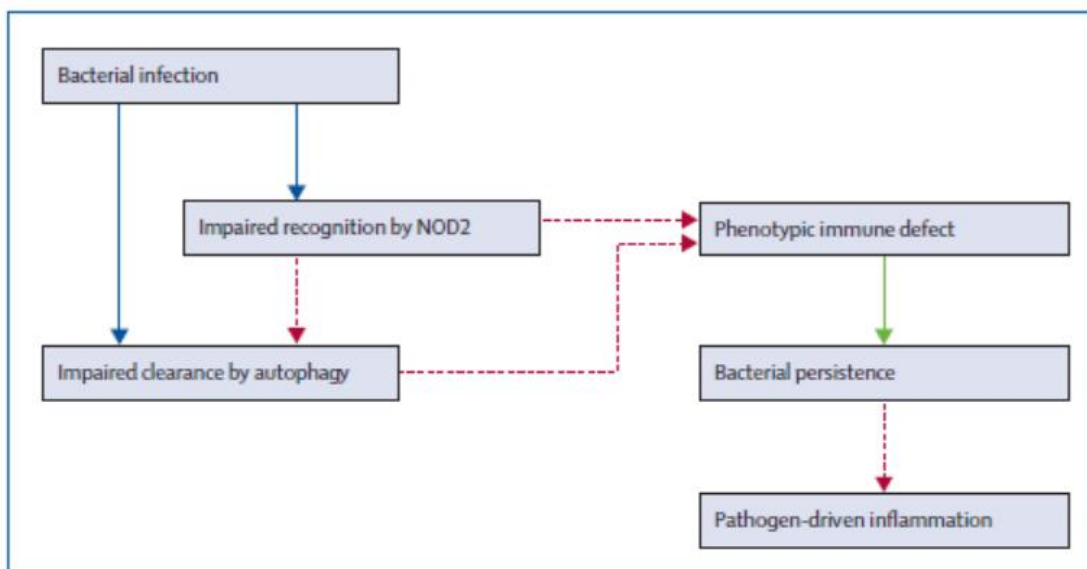
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Interleukins and tumour necrosis factor-alpha (TNF-alpha) have also been implicated in CD pathogenesis. CD is characterized by a T-helper type-1 cellular immune response pattern resulting in the production of interleukin 12 (IL-12), TNF, and interferon gamma (IFN-gamma). TNF has been shown to play a critical role in the inflammation in this disease and it has been found that an increased production of TNF by macrophages in CD patients results in increased concentrations of TNF in the stool, blood, and mucosa (Hanauer and Sandborn 2007).

Microbial

Thoreson (2007) found that organisms such as *Mycobacterium paratuberculosis*, *Pseudomonas* species, and *Listeria* species are implicated in the pathogenesis of CD. The inflammatory process involved in CD is as a result of a dysfunctional response to the infectious source (Thoreson and Cullen 2007). Coulombe and Behr (2009) recognized that complex genetic factors involved in CD and the role of immune deficiency and resulting phenotypic defects (Coulombe and Behr 2009) (Figure 12). They suggested a collaborative approach involving immunological and microbiological investigations in addition to genetic assessments to allow for a better understanding of the complex nature of CD (Coulombe and Behr 2009).

Figure 12. Crohn's disease as an immune deficiency (Coulombe and Behr 2009)



Environmental

It has been suggested that a variety of environmental factors influence CD. Smoking has been shown to double the risk, whereas in people who smoke, the risk of developing ulcerative colitis is less than in those who have never smoked (Thoreson and Cullen 2007).

Diet

Asakura *et al.* (2008) reviewed the association between food and intestinal microbes as potential causative factors of IBD. They reviewed epidemiological data and case-control studies published on Medline and found a positive association of animal meat, sweets and sugar with the occurrence of CD and UC. An analysis of Japanese epidemiological data suggested that the number of patients diagnosed with CD started to increase more than 20 years after an increased daily consumption of dietary animal meat and fats, and milk and dairy products, and after a decreased consumption of rice (Asakura, Suzuki *et al.* 2008).

D'souza *et al.* (2008) conducted case-controlled studies on population aged between 2.6 to 20 years of age and found that specific dietary patterns could be associated with higher or lower risks for CD in children. Foods found to be positively associated with CD were meats, fatty foods and desserts (D'Souza, Levy *et al.* 2008).

Psychosocial

It has been reported that there are discrepancies between disease activity and severity, and the patient's symptom experience and behaviour (Ringel and Drossman 2001). Discrepancies cannot be explained by biologic or morphologic findings, and usually are considered to be related to psychosocial factors. A survey conducted on 997 members of the Crohn's and Colitis Foundation of American with inflammatory bowel diseases found that physicians believed that psychosocial factors did not contribute to the cause of IBD (Drossman, Leserman *et al.* 1991), but they affect the clinical exacerbation of symptoms (Mitchell,

Guyatt et al. 1988). However, Caprilli (2006) reported that up to 50% of patients with CD have psychological disturbances and a lower quality of life (Caprilli, Angelucci et al. 2005).

In comparison, Robertson *et al.* (1989) found that patients with CD believed that psychosocial factors were a major contributor to the development of their disease (Robertson, Ray et al. 1989), with more than 90% thinking that stress was an influencing factor on disease activity (Rose, Walter et al. 2003). Ringel (2001) suggested that potential pathophysiologic mechanisms affecting CD activity included the direct stress effects on gut function, affected hypothalamic-pituitary-adrenal axis and neuroendocrine-immune regulation, stress-induced and centrally mediated inflammation, stress-induced and immune-mediated inflammation, and stress-induced increase in GI mucosa permeability (Ringel and Drossman 2001). Other psychosocial concomitant factors suggested include psychological diagnosis and mood states, and the impact of the disease on outcome – such as health-related quality of life and illness behaviour (Ringel and Drossman 2001; Rose, Walter et al. 2003).

II. B. 5. Investigations and Results

Comprehensive gastrointestinal assessment should involve detailed history taking, physical examination, and a range of investigations (Sathiyasekaran and Shivbalan 2006).

Investigations include laboratory studies, imaging studies and procedures (Walker-Smith 1994; Sathiyasekaran and Shivbalan 2006; Wu. G 2010). Laboratory studies may indicate the presence of inflammatory activity or nutritional deficiencies (Grossman. A 2009; Wu. G 2010). Anaemia may result from chronic inflammation, iron malabsorption, chronic blood loss and malabsorption of vitamin B-12 or folate (Wu. G 2010). Leukocytosis may result from chronic inflammation, abscess or steroid treatment and malabsorption may be reflected

by hypoalbuminemia, hypocholesterolemia, hypocalcemia, hypomagnesemia and hypoprothrombinemia (Wu. G 2010). Active CD activity can be also be assessed by the levels of acute inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) that can specifically evaluate Crohn's colitis (Lecis, Germana et al. 2002; Wu. G 2010).

Specific serological tests for identification of CD activity involve assessment of the presence *anti-Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear-staining antineutrophil cytoplasmic antibodies (p-ANCA) (Wu. G 2010). Increases in ASCA have been reported in up to 60% of CD patients (Vermeire, Van Assche et al. 2004). Russell *et al.* (2009) investigated the role of *anti-Saccharomyces cerevisiae* antibodies (ASCA) status and its relation to disease phenotypes in patients with IBD (Russell, Ip et al. 2009). Tests positive for ASCA and negative for p-ANCA suggests the presence of CD compared to UC and healthy controls (Russell, Ip et al. 2009; Wu. G 2010). A positive ASCA was also associated with OCD, perianal CD, presence of granulomata and markers of disease severity (Russell, Ip et al. 2009). Positive levels of p-ANCA are commonly found in UC (Lecis, Germana et al. 2002).

Testing of stool samples should be routinely conducted. It can be assessed for pathogens, ova, parasites and *Clostridium difficile* toxin to eliminate potential infectious aetiological factors during relapses of CD and prior to commencing immunosuppressive therapies (Wu. G 2010).

In CD the radiographic findings may not correlate well with disease activity (Walker-Smith 1994). Recommended imaging includes barium contrast studies, computed tomography

(CT), magnetic resonance imaging (MRI), ultrasonography, endoscopic ultrasonography and radionucleotide scanning. Barium contrast studies are ideal for defining the nature, distribution and severity of CD (Wu. G 2010). Contrast studies are more likely than endoscopic studies to identify fistulas. Transmural inflammation and fibrosis lead to limited distensibility with decreased luminal diameter and stricture formation. Like fistulas, strictures are more easily appreciated on radiographic studies than by endoscopy (Sathiyasekaran and Shivbalan 2006).

CT may be used for assessment of extramural complications such as fistulas, abscesses, fluid collections, assessment of the thickness of bowel walls and mucosal damage, hepatobiliary and renal complications (Wu. G 2010). Similarly ultrasonography can enable detection of enlarged lymph nodes, abscesses, stenoses and fistulae. MRI can be used to differentiate between active inflammation and fibrosis, and identify inflammatory and fibrostenotic lesions (Wu. G 2010). Perianal disease can be evaluated with use of rectal endoscopic ultrasonography and radionucleotide scanning may aid assessment of the severity of CD in patients unable to have colonoscopy or barium studies (Wu. G 2010).

Endoscopic investigation can enable differentiation of CD from peptic ulcer disease and detect complications of CD such as aphthous ulcers (Wu. G 2010). These ulcers are small in diameter and surrounded by a thin red halo of oedematous tissue. Ulcers may be rounded or long and serpiginous. Longitudinal and transverse ulcers may intersect to form a grid with intervening cobblestone-like areas of non-ulcerated mucosa. Large, deep, penetrating ulcers can be surrounded by areas of normal-appearing mucosa (Grossman. A 2009). Endoscopies can also enable identification of diffuse mucosal irregularities of erythema, oedema, and

granularity indicating upper GI tract inflammation that may be present in the absence of upper GI symptoms (Grossman. A 2009).

Colonoscopy is invaluable and considered a standard procedure in CD investigation (Grossman. A 2009), performed for assessment of CD activity and disease complications (Sathiyasekaran and Shivbalan 2006). Colonoscopy is useful for obtaining colonic and ileal biopsies for histopathological assessment (Wu. G 2010). The rate of granuloma detection in intestinal lesions has been reported to be as high as 71% (Plauth, Jenss et al. 1991).

New investigation modalities such as double balloon enteroscopy, wireless capsule endoscopy (with better results in adults), and use of gadolinium enhanced MRI to differentiate between CD and UC have been used. However no data is available about the use of these techniques in a paediatric population (Sathiyasekaran and Shivbalan 2006). Abdominal ultrasound can also be used to detect hepatomegaly and any marked enlargement of the mesenteric lymph nodes or thickening of intestinal wall (William, Marsch et al. 2007).

Oral Crohn's Disease

Investigation of OCD is the same as that for OFG. Recommendations for systematic examination by clinicians experienced with oral pathology for greater accuracy in identification of lesions presenting with CD. Harty *et al.* (2005) and Pittock *et al.* (2001) found that less than 50% of children with disease-specific lesions were accurately identified by gastroenterologists (Pittock, Drumm et al. 2001; Harty, Fleming et al. 2005). They recommended that in addition to the routine laboratory and imaging studies, there should be systematic clinical assessment of the oral cavity including the submandibular lymph nodes, lips, labial mucosa and sulci, commissures, buccal mucosa and sulci, gingival, tongue, floor of

mouth, and hard and soft palate (Pittock, Drumm et al. 2001; Harty, Fleming et al. 2005). Oral biopsy specimens should be taken when clinically indicated (Harty, Fleming et al. 2005). Oral lesions are ideal sites for initial investigation for CD as oral lesions commonly contain granulomas (71%) (Plauth, Jenss et al. 1991) and are easily accessible for diagnostic biopsies (Harty, Fleming et al. 2005).

Savage *et al.* (2004) investigated whether OFG could be distinguished immunologically from CD by comparing non-specific and specific aspects of humoral immunity in serum, whole saliva and parotid saliva in three groups of patients. They found non-specific immunoglobulin levels (Serum IgA, IgA1 and IgA2 subclasses) in both whole saliva and parotid saliva are raised in patients with OFG, with or without gut inflammation (Savage, Barnard et al. 2004). Salivary IgA (and IgG) levels were raised in OFG and OFG + CD, but not in the CD group. Parotid IgA was also raised in OFG and OFG + CD but not in CD. Serum IgA antibodies to *S. cerevisiae* were raised markedly in the two groups with gut disease while serum IgA (or IgG) antibodies to *C. albicans* were elevated significantly in all three patient groups (Savage, Barnard et al. 2004).

These results suggest salivary gland involvement in OFG, whereas serum IgA reflects mucosal inflammation anywhere in the GI tract. Whilst no differences were found with antibodies to *S. mutans*, there were raised levels of saliva IgA antibodies to *S. cerevisiae* (and *C. albicans*) (Savage, Barnard et al. 2004). This suggested that raised serum IgA antibodies to *S. cerevisiae* may reflect gut inflammation, whereas elevated saliva IgA antibodies to *S. cerevisiae* or raised IgA or IgA2 levels in saliva reflect oral but not gut disease. These findings are significant as antibody titres from saliva can be used as a marker of coincident

gut disease in those with OFG. Due to the accessibility and non-invasive nature of saliva collection, it can be widely used as a progress screen to investigation potential development of CD (Savage, Barnard et al. 2004).

II. B. 6. Histopathology

CD is microscopically characterized by the presence of aphthoid ulcers, fissure ulcers, transmural inflammation, fistulas, lymphangiectasia, fibrous structuring and neural changes through the GI tract (Geboes and De Hertogh 2003; Valusek. P 2010). Early mucosal lesions are focal in nature, including epithelial patchy necrosis, aphthoid ulcer or mucosal micro-ulcerations involving the loss of 1-6 cells. There is also limited necrosis of surface epithelial cells and the presence of microgranulomas that are usually situated in the upper part of the mucosa. Other features include the location of ulcerations at the base of crypts with neutrophils extending into the bowel lumen and damage of small capillaries (Geboes 2001). There may also be abnormalities of the villi including structural irregularity, blunting or broadening, in addition to preserved or increased mucin production by epithelial cells, mucoid or pseudopyloric metaplasia, active chronic inflammation and the presence of granulomas (Geboes 2001).

Biopsies of early lesions do not yield essential diagnostic information, with the exception of aphthoid ulcers that commonly have the histological characteristics of granulomas and are considered to be diagnostics for CD (Geboes 2001). Other features include proliferative stromal and nodular inflammatory changes in the bowel wall, leading to a thick, firm appearance and, ultimately, strictures (Geboes 2001). The presence of ileal lesions enables discrimination of CD from UC (Sanders 1998).

Granulomas can be found in otherwise healthy mucosa or in inflamed tissues. They may develop in all layers of the intestine from the mucosa to serosa but are most commonly found in the submucosa (Geboes 2001). They may also be located in draining lymph nodes in 20 to 50% of cases (Cook 1972; Geboes and De Hertogh 2003). In adults, it has been reported that the frequency of finding granulomas in CD is highly variable, from 15 to 85% (Geboes and De Hertogh 2003).

In children, higher numbers of granulomas are observed, with the incidence twice as high as those found in adults. This number is reduced in the second year of the disease and after the age of 16 years. Geboes (2003) reported that the presence of granulomas in 26 to 42% of patients (Geboes and De Hertogh 2003). Pittock *et al.* (2001) reported that granulomas were found more frequently in oral CD tissue than anywhere else in the GI tract, with 29% of patients with colonic involvement had granulomatous inflammation taken from abnormal tissue and 75% of biopsy specimens from abnormal oral mucosa contained granulomas (Pittock, Drumm et al. 2001).

Immunohistochemical features of CD include the expression of various cytokines and mediators such as interleukin-10, interleukin-12, interleukin-15 and tumour necrosis factor alfa (TNF-alfa) (Geboes and De Hertogh 2003).

General Histology

Noncaseating granulomas are characteristic but not pathognomonic of CD (Geboes and De Hertogh 2003). In these lesions, macrophages are arranged in clusters and are large cells with large oval nuclei and abundance of pale eosinophilic cytoplasm (Valusek. P 2010). Other

histological features include epithelioid granulomas, relatively unchanged crypts or segmental distribution of crypt atrophy and crypt distortion together with discontinuous focal or patchy inflammation and mucin preservation in the epithelium at the ulcer edge, and the presence of normal and inflamed sampled of tissue (Chambers and Morson 1979). Some granulomatous lesions have giant cells containing calcified conchoids bodies (Geboes and De Hertogh 2003). Inflammatory cells present include lymphocytes- mainly CD4+ T cells, showing expression of CD28 and the ligand for the B7-related cell surface proteins and CD86 (Geboes and De Hertogh 2003).

It is recognized that most studies of histological features of IBD have been performed in adults (Geboes and De Hertogh 2003). It is speculated that there is a difference in histological features of CD in children, such as the prevalence of discontinuous inflammation and density of infiltration in specimens (Geboes and De Hertogh 2003).

The results of biopsies are ultimately dependent on tissue sampling, taking into account the number of biopsies taken, number of sections examined, site of biopsy, and the nature of the samples i.e. endoscopic or surgical (Geboes and De Hertogh 2003). It is recognized that not all histological features can be detected in biopsy specimens, thus for diagnosis microscopic features of IBD are considered (Geboes and De Hertogh 2003). It is suggested that diagnosis of CD should be based upon the presence of an epithelioid granulomas with one other feature suggestive or diagnostic for IBD, or the presence of three other features in the absence of granulomas, provided that specific infection has be excluded (Geboes and De Hertogh 2003).

Oral Crohn's Disease

William *et al.* (2007) reported that oral histological changes may correspond with those seen elsewhere in the GI tract. Histopathology from a lower lip mucosa biopsy found focal collections of lymphocytes in the epithelium with loose lamina propria and collections of macrophages in the superficial tissue layers. In the deeper layers there were mixed-cell intramural infiltration of lymphocytes and plasma cells in blood with lymph vessels and mild interstitial plasmacytosis (William, Marsch *et al.* 2007). In the same patient, granulomas were found in the ileal mucosa and in other segments of the colon (Ghandour and Issa 1991). Oral biopsies may also show marked epithelial hyperplasia, with intense chronic inflammation in the submucosa with foci for granulomatous inflammation with no caseation (Ghandour and Issa 1991).

II. B. 7. Management

There are general guidelines for the management of CD due to the varying severity and disease activity i.e. anatomic locations, clinical manifestations, and gastrointestinal complications such as fistulas, abscesses, strictures, and perforations (Sathiyasekaran and Shivbalan 2006; D'Haens, Vermeire *et al.* 2008). Response to therapy is monitored by empirical clinical assessment directed at the problem that is most troublesome for the patient (Sathiyasekaran and Shivbalan 2006). A common problem in the management of CD is a marked discrepancy between the severity of the patient's symptoms and the objective signs of disease activity (D'Haens, Vermeire *et al.* 2008).

Pharmacotherapy in CD is aimed at reducing morbidity, prevent complications and maintain nutritional status. Other forms of therapy include modification of the diet and when indicated, surgical intervention (Grossman and Baldassano 2008).

When treating children with CD, the general aims of treatment are to achieve the best possible clinical, laboratory, and histological control of the inflammatory disease with the least adverse effects from medication. It is also important to promote growth with adequate nutrition, and aid the child to function as normally as possible with minimal psychosocial concerns (Sauer and Kugathasan 2009). Treatment has changed over the past few years, reflecting the development of new agents that can target specific locations in the GI tract and specific cytokines (Grossman and Baldassano 2008).

Active Disease

Pharmacotherapy

The recommended first-line therapy for CD are either oral corticosteroids (prednisone) or antibiotics (metronidazole and/or ciprofloxacin) (D'Haens, Vermeire et al. 2008). Infliximab is typically given in combination with immunosuppressant medication (e.g. azathioprine) to patients who have failed therapy with azathioprine or 6-MP (Sandborn and Hanauer 2002; Sandborn, Feagan et al. 2007). Patients who respond to parenteral corticosteroids are switched to high-dose oral corticosteroids (prednisone, 40 mg/day), and the dose of prednisone is gradually reduced. Patients with severe CD who do not respond to parenteral corticosteroids within a week should be considered for surgery (Hanauer, Feagan et al. 2002).

Typically, therapy for paediatric CD is administered in a step-up approach. Patients with mild disease are treated with preparations of mesalazine, antibiotics, and nutritional therapy. If no response occurs or if disease is more severe than initially thought, corticosteroid and immunomodulatory therapy (mercaptopurine or methotrexate) is attempted. It should also be noted that the use of azathioprine in children is controversial, particularly in adolescent males due to the association with hepatosplenic lymphoma which is almost universally fatal. In more severe cases, biologic and surgical therapy is indicated (Grossman. A 2009).

Diet

Patients with CD should aim for maintaining a balanced diet (Afzal, Van Der Zaag-Loonen et al. 2004). Fibre supplementation may be required with individuals with colonic disease and may be beneficial by aiding colonic mucosal healing. Alternatively a low-roughage diet is usually indicated for patients with obstructive symptoms (Afzal, Van Der Zaag-Loonen et al. 2004; Wu. G 2010). During the course of CD, some patients develop lactose intolerance and may require calcium supplements as a result. A low-fat diet with the addition of medium-chain triglyceride preparations is indicated for individuals who have had extensive resection of the terminal portion of the ileum (Grossman and Baldassano 2008).

An elemental diet has been recommended to induce remission in acute CD (Afzal, Van Der Zaag-Loonen et al. 2004). Studies have indicated a lower rate of disease relapse when patients were on a diet with consumption of at least 1200 kcal/day. The disease was found to relapse following resumption of a normal diet (Afzal, Van Der Zaag-Loonen et al. 2004). In other reports, following a relapse in symptoms, a total elemental diet was introduced with resolution and maintenance of symptoms (Sweatman, Tasker et al. 1986).

Maintenance Therapy

Maintenance therapy with aminosalicylates has been recommended for those brought into remission with corticosteroids or by surgery (Hyams, Lerer et al. 2009). Maintenance with mercaptopurine or azathioprine is recommended for patients brought into remission with these drugs or who were corticosteroid dependent and then converted to these drugs (Juillerat, Pittet et al. 2007). In paediatric CD management it is believed that there is no role for corticosteroids as maintenance or long term therapy due to the significant adverse effects and complications in children (Juillerat, Pittet et al. 2007).

Surgical Therapy

Within 10 years of diagnosis, approximately 70% of patients with CD undergo surgery for their disease (Fazio, Tjandra et al. 1993). Because surgical resection is not curative of CD and recurrences are likely with reoperation required in 70-90% of all patients and multiple procedures in more than 30% (Duepre, Senagore et al. 2002). Failure of medical management is a common cause for resection in patients with CD. Developments of complications such as obstruction, fistulas and/or abscesses are often indications for resection in CD (Fazio, Tjandra et al. 1993). The incidence of recurrence severe enough to need repeat surgery after ileal or ileocolic resection is about 50% after 10 years and 75% after 15 years (Duepre, Senagore et al. 2002).

Complications

Abscesses and fistulas are common complications in CD (Uchikoshi, Nishida et al. 2006). Leakage of intestinal contents through a fissure into the peritoneal cavity results in an abscess. Extension of the inflammatory process through the wall of adjacent viscera or

through the abdominal wall to the exterior results in a fistula (Vatn 2009). Abscesses occur in 15 to 20% of patients with CD and are especially common in the terminal ileum (Vatn 2009). The typical clinical manifestation of an intra-abdominal abscess is fever, abdominal pain, tenderness, and leukocytosis (Wu. G 2010).

The prevalence of fistulas is 20 to 40% in CD (Vatn 2009). Most fistulas are enteroenteric or enterocutaneous, with smaller numbers being enterovesical or enterovaginal. Total parenteral nutrition or immunomodulator therapy may induce fistula closure; however, the fistulas often recur after the total parenteral nutrition or immunomodulator therapy is stopped. Surgical treatment includes resection of the segment involved with active disease (Vatn 2009).

Obstruction is a common complication of CD, particularly in the small intestine, and is a leading indication for surgery (Vatn 2009; Wu. G 2010). Small bowel obstruction in CD may be caused by mucosal thickening from acute inflammation, by muscular hyperplasia and scarring as a result of previous inflammation, or by adhesions (Sathiyasekaran and Shivbalan 2006). Obstruction may also occur because of impaction of a bolus of fibrous food in a stable, long-standing stricture. Obstruction is marked by cramping abdominal pain and diarrhoea that worsen after meals and resolve with fasting. Strictures may be evaluated by oral contrast studies, barium enema, or colonoscopy, depending on the anatomic location (Vatn 2009).

Gerson *et al.* (2000) reported that medications used in management of IBD are often problematic for patients. In particular, corticosteroids cause emotional fragility, increased appetite and weight gain, Cushingoid facies, hypertension, and muscle weakness (Gerson and Triadafilopoulos 2000). Drugs for management of diarrhoea have been reported to have sedative effects and xerostomia. The physical burden of the disease has a profound effect on

the quality of life. This includes loss of energy and malaise that may have a greater effect than the bowel symptoms themselves. Psychological impairments include anxiety, anger, irritability and depression. In a group of adult patients with IBD, 50% report exacerbations of their illness causes significant stress in their lives (Gerson and Triadafilopoulos 2000).

Recommendations were made for provision of palliative care to improve the patient's quality of life. This includes provision of relief from pain and other distressing symptoms (Gerson and Triadafilopoulos 2000). The availability of a support system for patients and their families was advised, to help them cope with illness and lead functional lives. Other forms of palliative care should specifically manage oral and skin ulcerations, stomal problems, control of nausea and vomiting, management of chronic diarrhoea and anal pruritus, anaemia, treatment of steroid related bone disease and psychological problems (Gerson and Triadafilopoulos 2000).

Direct oral problems affecting patients include a dry mouth due to poor oral intake and/or dehydration. Opportunistic infections such as candidiasis may arise following corticosteroid and immunosuppressant therapy. In a review by Gerson *et al.* (2000), management includes use of nystatin suspension (4/day) for 10 days, ketoconazole 200mg daily for 5 days, or a single dose of fluconazole. Severe aphthous ulcers can be treated with oral metronidazole 500mg twice a day for 7-10 days, betamethasone 0.5mg in 5mL of mouth wash, or tetracycline 250mg in 5mL of mouth wash (Gerson and Triadafilopoulos 2000).

Treatment of OCD is the same as that for OFG, involving variable therapeutic regimens. Management approaches range from diet therapy (White, Nunes et al. 2006), and/or topical application of a topical steroid preparation alone such as 0.1% triamcinolone acetonide in

Orabase, or in combination with antifungal medications (Sciubba and Said-Al-Naief 2003). Intralesional therapy with injections of high concentrations of delayed-release triamcinolone acetonide (0.1%) (Mignogna, Fedele et al. 2001; Mignogna, Fedele et al. 2003) may be indicated. Systemic therapy may already be required for management of CD manifestations at other sites within the GI tract. Therapy would involve short term oral steroids combined with antibiotics and/or immunosuppressants (Dummer, Lurz et al. 1999; Bogenrieder, Rogler et al. 2003; Galbraith, Drolet et al. 2005). For severe OCD cases with little response to systemic steroids, thalidomide therapy (Hegarty, Hodgson et al. 2003) and/or surgical therapy may be indicated (Worsaae, Christensen et al. 1982).

IV. Association between Orofacial Granulomatosis and Crohn's Disease

It is recognized that OFG and CD share a number of clinical and histological features for example the presence of noncaseating granulomatous inflammation (Grave, McCullough et al. 2009), but the relationship of the two conditions is still unclear (Saalman, Mattsson et al. 2009). It has been proposed that OFG may be under or misdiagnosed, and its course may be either independent of or preceding CD (Bogenrieder, Rogler et al. 2003). However, it has been found that oral lesions in OFG and OCD are macroscopically and histologically similar to lesions found in the intestine. Both feature linear ulcerations, lymphoedema with induration with associated cobblestone appearance, small numbers of noncaseating granulomas, and pseudopolyps (Scully, Cochran et al. 1982; Dummer, Lurz et al. 1999).

Freysdottir *et al.* (2007) found that the Th1 environment within the oral tissues resemble that observed in gut CD tissues, suggesting that some OFG patients have both histopathological and immunopathological features that resemble those in CD patients (Freysdottir, Zhang et al. 2007). Basu *et al.* (1974) similarly found that oral lesions macroscopically and histologically

resembled those seen in the GI tract in CD, suggesting that it was due to the same disease process (Basu, Asquith et al. 1974).

Sanderson *et al.* (2005) disputed the link between OFG and CD, stating that high proportion of granulomas in OFG may suggest OFG and CD are different conditions. It has been suggested that OFG associated intestinal inflammation may represent a separate entity in which granulomatous inflammation occurs throughout the GI tract in response to an unknown antigen(s) (Sanderson, Nunes et al. 2005). This was based on the higher presence of granulomas in oral biopsies compared to intestinal CD biopsied (Sanderson, Nunes et al. 2005).

Pittock *et al.* (2001) and Harty *et al.* (2005) found that paediatric patients with OFG presented for investigation soon after onset of symptoms, and 50% had nil gastrointestinal symptoms but were diagnosed with CD initially or thereafter (Pittock, Drumm et al. 2001; Harty, Fleming et al. 2005). Additionally OFG patients with no gut symptoms were commonly found to have endoscopic and histological intestinal abnormalities (Pittock, Drumm et al. 2001; Harty, Fleming et al. 2005). This finding is supported by Sanderson *et al.* (2005) who found that younger patients with OFG were more likely to have concomitant interlineal involvement (Sanderson, Nunes et al. 2005). In these patients, granulomas are more frequent in endoscopic biopsies than reported in patients with documented CD. From this group, granulomas were found to be present in 68% of cases (Sanderson, Nunes et al. 2005).

Khouri *et al.* (2006) also reported that there appears to be a likely relation between CD and OFG. He found that with paediatric OFG patients, when present and aetiologies of allergies

and infections were excluded, it was related to CD (Khouri, Bohane et al. 2005). Saalman *et al.* (2009) reported similar findings with 50% of paediatric patients presenting with OFG being diagnosed with CD during follow-up (Saalman, Mattsson et al. 2009).

If oral lesions are present, they may be helpful in the diagnosis of CD, as granulomatous inflammations in oral sites are more frequently detected (Pittock, Drumm et al. 2001). As the orofacial region is directly visible, the sites involved are also considered to be easier to access for biopsies compared to other sites in the gastrointestinal tract which would otherwise require more invasive procedures (Pittock, Drumm et al. 2001; Harty, Fleming et al. 2005). It is recommended that a systematic oral examination in addition to gastrointestinal investigations be undertaken, as they are valuable as part of the initial diagnostic evaluation of children with suspected CD (Bogenrieder, Rogler et al. 2003; Harty, Fleming et al. 2005; Khouri, Bohane et al. 2005; Saalman, Mattsson et al. 2009).

CONCLUSION

The incidence of orofacial granulomatosis in a paediatric population is becoming increasingly recognized (Leao, Hodgson et al. 2004). Despite having a variable clinical presentation it is recognized that it encompasses characteristics of other systemic diseases. Even though OFG often presents with sub-clinical symptoms that are self-resolving, underlying systemic conditions that are related have significant health implications if they are not correctly managed.

Published literature reports an increasing incidence of CD in a paediatric population over recent decades. With its variable clinical presentation, differing phenotype between paediatric and adult groups, and the chronic nature of CD, early diagnosis and correct management is important. Early intervention is aimed at preventing and minimizing complications associated with growth and development, systemic manifestations, impaired quality of life, psycho-social complications over a life time.

Establishing a relationship between OFG and CD, and improving accuracy in recognizing disease-specific oral lesions is important in diagnosis of the disease (Rowland, Fleming et al. 2009). It is important to recognize that the mouth is a useful source of diagnostic material that is easily accessible for non-invasive examination. Additionally, due to the aesthetic implications from the clinical presentation of OFG it is recognized that affected individuals are more likely to seek care at an earlier stage when compared to CD patients with normal or sub-clinical gastrointestinal symptoms, thus resulting in care being sought an earlier stage.

Investigation, diagnosis and appropriate management of suspected OFG and CD should involve a multi-disciplinary approach with close collaboration between gastroenterologists and a dentist or oral medical specialist. There is evidence supporting that it is difficult for non-expert clinicians to accurately identify oral signs of CD such as mucogingivitis, with

under diagnosis of OFG (Pittock, Drumm et al. 2001; Harty, Fleming et al. 2005; Rowland, Fleming et al. 2009).

Whilst present literature does not support that all patients with OFG will progress to develop CD elsewhere in the intestine, further investigation can be sought into the incidence, prevalence and phenotype of OFG in CD in a paediatric population. Additionally, a visual guide can be developed to aid diagnosis of OFG by non-dental health care workers, thus improving the standard of health care that can be provided to affected individuals.

Chapter III

Article 1 (Scientific Article)

*A clinical study of oral manifestations in a South Australian paediatric population with
Crohn's Disease*

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Abstract

Background: The aim of this pilot study is to determine if oral manifestations, including orofacial granulomatosis (OFG) are a precursor to, or an oral manifestation of paediatric Crohn's Disease (CD), or a separate pathological condition in a paediatric Australian population. From the national data 8.6 – 9.3% of paediatric patients diagnosed with Crohn's Disease have oral involvement.

Methods: Retrospective analysis was undertaken of the patients on the Australian Paediatric and Adolescent Inflammatory Bowel Disease Database and medical records of those patients with CD or OFG from the Paediatric Dental Unit, WCH (n=945). From this retrospective analysis, a cohort of 22 eligible South Australian paediatric patients participated in a clinical study to assess active OFG and/or CD.

Results: Of the cohort of paediatric patients assessed in this study, 54.5% of patients presented with oral involvement. The mean age of CD diagnosis was 11 years and 4 months, while the mean age of OFG diagnosis was 9 years and 6 months.

Conclusions: These results indicate that oral involvement maybe more common than the national data indicates and that it may both precede and be an oral manifestation of CD. It also indicates the importance of collaboration of dental and medical physicians to aid in early diagnosis of Crohn's Disease.

Key Words: Orofacial granulomatosis, oral Crohn's disease, Crohn's disease

Abbreviations and acronyms: OFG = orofacial granulomatosis, OCD = oral Crohn's disease, CD = Crohn's disease,

Introduction

Orofacial granulomatosis (OFG) is the term given to a group of diseases characterised by noncaseating, granulomatous disorder involving oral and maxillofacial soft tissues.

Wisniewski *et al.* (1985) described OFG to encompass widely variable presentations of multiform, temporary and chronic clinical findings from oral Crohn's disease (CD), oral sarcoidosis, Melkersson Rosenthal syndrome (MRS) and cheilitis granulomatosa (CG) of Miescher (Grave, McCullough *et al.* 2009). Other diseases that may present with chronic facial swelling include hypersensitivity reactions, acquired and hereditary angioedema, Hansen's disease (leprosy), deep fungal infections, Anderson-Fabry disease and Ascher's syndrome (Mignogna, Fedele *et al.* 2003). According to classifications of granulomatous diseases, OFG is considered an immunological aberration, as the causative agent or antigenic insult is unrecognized (James 2000).

OFG involves granulomatosis of atypical sites of the orofacial region such as one or both lips, chin, cheeks, peri orbital, zygomatic tissues, lymph nodes, eyelids and forehead, and may present with single or multiple minor manifestations unilaterally or bilaterally (Mignogna, Fedele *et al.* 2003). Cheilitis granulomatosa (labial enlargement) is the most common clinical presentation, followed by oral ulcerations. Oral ulcerations are most commonly found in the buccal or labial vestibular sulci or mucosa. There is wide variety in the type of ulcerations, ranging from deep linear ulcerations with a characteristic well defined erythematous raised border, to superficial ulcerations, which may occur on any other mucosal surface⁴. In addition, other oral signs include; angular cheilitis and fissuring of the lips, mucosal swelling, mucosal tags, cobblestone buccal mucosa, gingival enlargement and fissuring of the tongue. In addition, craniofacial neurological and neuro-vegetative manifestations such as facial nerve palsy, facial swelling, erythema, and less commonly

cervical lymphadenopathy have also been known to occur (Sweatman, Tasker et al. 1986; Leao, Hodgson et al. 2004; Sanderson, Nunes et al. 2005).

Crohn's disease is a form of chronic inflammatory bowel disease (IBD) that is a transmural process producing focal ulcerations throughout the gastrointestinal (GI) tract. It most commonly involves the terminal ileum, but also presents at any point of the alimentary canal from the mouth to the anus (Ravikumara and Sandhu 2006). It has been documented that there has been an increasing frequency of incidence of CD in a paediatric population, with 20-30% of CD patients being diagnosed before the age of twenty (Phavichitr, Cameron et al. 2003).

It is recognized that OFG and CD share a number of clinical and histological features (Grave, McCullough et al. 2009), but the relationship of the two conditions is unclear (Saalman, Mattsson et al. 2009). It has been proposed that OFG may be under or misdiagnosed, and its course may be either independent of or precede CD (Bogenrieder, Rogler et al. 2003). It has been found that oral lesions in CD (oral CD; OCD) and OFG are macroscopically and histologically similar to lesions found in the intestine. Both feature linear ulcerations, lymphoedema with induration with associated cobblestone appearance, small numbers of noncaseating granulomas, and pseudopolyps (Scully, Cochran et al. 1982; Dummer, Lurz et al. 1999). In recent retrospective studies, it was found that paediatric patients with OFG presented for investigation soon after onset of symptoms, and 50% had no gastrointestinal symptoms but were diagnosed with CD initially or thereafter (Pittock, Drumm et al. 2001; Harty, Fleming et al. 2005). Additionally OFG patients with no gut symptoms were commonly found to have endoscopic and histological intestinal abnormalities (Pittock, Drumm et al. 2001; Harty, Fleming et al. 2005).

If oral lesions are present, they may be helpful in the diagnosis of CD, as granulomatous inflammations in oral sites are more frequently detected (Pittock, Drumm et al. 2001). As the orofacial region is directly visible, the sites involved are also considered to be easier to access for biopsies compared to other sites in the gastrointestinal tract which would otherwise require more invasive procedures (Pittock, Drumm et al. 2001; Harty, Fleming et al. 2005). It has been previously recommended that a systematic oral examination in addition to gastrointestinal investigations be undertaken, as they are valuable as part of the initial diagnostic evaluation of children with suspected CD (Bogenrieder, Rogler et al. 2003; Harty, Fleming et al. 2005; Khouri, Bohane et al. 2005; Saalman, Mattsson et al. 2009).

This study aims to determine if orofacial granulomatosis and other oral manifestations are a precursor to, or an oral manifestation of paediatric Crohn's Disease, and whether earlier diagnosis can be made through oral changes.

Methods

A cohort of paediatric patients were recruited from The Australian Paediatric and Adolescent Inflammatory Bowel Disease Database (APAIBDD) and the Paediatric Dental Unit (PDU), Women's and Children's Hospital (WCH). The APAIBDD is a prospective national IBD databased that was established to assess the epidemiology and phenotype at presentation of paediatric patients (aged sixteen years and younger) with IBD. Data was collected through tertiary medical institutions by physicians in paediatric gastroenterology units. The data from the APAIBDD included in this study was accessed by the supervising paediatric gastroenterologist. The inclusion criteria included South Australian patients from the Departments of Gastroenterology and Paediatric Dentistry who were aged sixteen-years-old

or younger, who had signs and symptoms and a diagnosis consistent with CD (with or without oral symptoms) and/or OFG (n=58). From the sample of 58 patients, one was diagnosed with OFG only and 6 had previously been diagnosed with both OFG and CD, The exclusion criteria included patients who were over the age of 16 years, unable to co-operate with having a clinical assessment and those who had a change of diagnosis to ulcerative colitis. Ethics approval was obtained from the Human Research Ethics Committee (HREC) from the Childrens Youth and Women's Health Service (CYWHS) (REC2111/10/11) (See Appendix I). Information packages and consent forms were sent to all patients and their parents/guardians. Over a period of 14 months (from January 2009 to March 2010) a single investigation was conducted following a standardised protocol for dental clinical assessment (Appendix II) questionnaires and clinical assessments were conducted on the twenty two (22) patients (n=22/58) who consented to participate in this study. Data collection included patient/parent questionnaire (Appendix III), clinical examination (Appendix IV), use of an OFG/Oral manifestations disease activity index (Appendix V), clinical photography (Appendix VI) and serological investigation (Appendix II).

Information was recorded prospectively on each patient at the clinical assessment appointment by the primary researcher, through the clinical assessment and patient questionnaire. This information was collected to determine oral manifestations and/or CD disease activity as the time of examination. Clinical examination was performed on each patient and findings including weight and height were recorded. Intra-oral and extra-oral clinical examination were carried out by two paediatric dentistry registrars based on a modified World Health Organisation 'Oral Health Surveys: Basic Methods 4th Edition' protocol (1997). Digital intra-oral and extra-oral photographs were taken on the day of the clinical examination. Blood samples were taken for full blood count, inclusive of iron levels,

Vitamin B12, ESR, and liver function tests including C-reactive protein. Specific requests were made to assess the levels of anti-Saccharomyces cerevisiae antibodies (ASCA), anti-neutrophil cytoplasmic antibodies (ANCA) and ANCA with perinuclear staining (p-ANCA). An OFG/Oral manifestations disease activity index (Appendix V) was devised by the researchers and used to assess and evaluate extra and intra oral disease activity. The sites listed are common locations for OFG / OCD manifestation and can easily be assessed during clinical evaluation.

Data were analysed using SPSS Statistics Data Editor for Windows™. Comparison between groups was made using 91.3% confidence intervals for categorical variables and descriptive statistics.

Results

Retrospective Occurrence of Crohn's Disease and Oral Manifestations

Retrospective analysis of the APAIBDD found that over a seventeen-year period (1992-2009), 945 paediatric patients were diagnosed with Crohn's disease in Australia. The number of paediatric patients diagnosed with Crohn's Disease in South Australia during that time frame was 173 (18.3%), with a mean age of 12.8 years (SD 3.6, range 1.1-24.2 years) at the time of diagnosis. This group consisted of 109 males (109/173, 63.0%) with a mean age of 12.6 years (SD 3.8, range 1.1-24.2 years) and 65 females (65/173, 37.6%) with a mean age of 13.2 years (SD 3.2, range 3.4-19.2 years). Further analysis of the APAIBDD found that nationally, 8.6% of paediatric CD patients have oral manifestations (81/945), while in South Australia, 9.3% of paediatric patients diagnosed with CD were recorded as having had oral manifestations (16/173) at the time of their gastroenterological consultation.

Prospective Questionnaires and Clinical Assessment

A total of twenty-two (22) participants were included in the study. The mean age at the time of assessment was 13 years and 4 months (13.33 years, SD 3.6, range 4.67- 16.67years).

From this group fourteen males and seven females were diagnosed with CD, and one male was diagnosed with OFG. At the time of clinical assessment 19 patients (86.4%) were undergoing therapy for their active CD and symptoms.

Relevant medical findings, including Gastrointestinal

The reported CD symptoms included; lethargy (n = 20, 90.9%), weight loss (n = 19, 86.4%), abdominal pain (n = 18, 81.1%), malaise (n = 16,72.7%), diarrhoea (n = 15, 68.1%), bloating (n = 15, 68.1%), melena (n = 14,63.6%) and constipation (n = 5, 22.7%). Other reported symptoms included reflux (n = 1), joint pain (n = 2), rash (n = 1), vomiting blood (n = 1), headaches (n = 1), and recurrent fevers (n = 3). Perianal changes were reported in almost half of the patients (45.5%) with concomitant symptoms including anal abscesses (n = 6), anal fistulas (n = 2), anal fissures (n = 8), and anal tags (n = 9). The mean age of the reported first GI symptoms was 8 years 9 months (SD 4.4 years, range, 0.08- 15.08 years), however, the mean age of CD diagnosis was 11 years and 4 months (SD 3.56 years, range, 3.46-15.94 years, CI 91.3%). (Table 1)

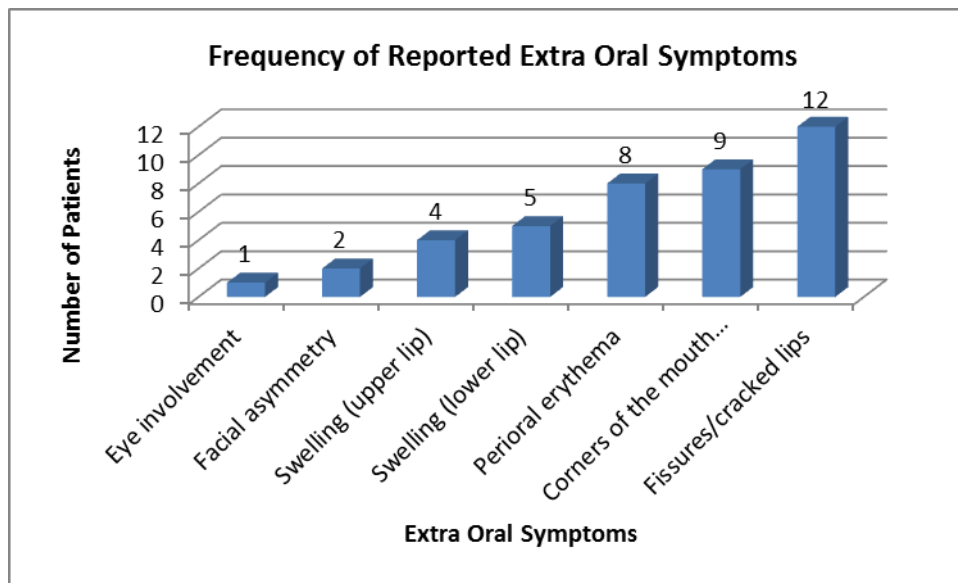
Table 1. Summary of reported gastrointestinal signs

Signs	Number (n)	Percentage (%)
Lethargy	20	90.9
Weight loss	19	86.4
Abdominal pain	18	81.1
Malaise	16	72.7
Diarrhoea	15	68.1
Bloating	15	68.1
Constipation	5	22.7
Perianal changes		
Abscess(s)	6	27.3
Fistula	2	9.1
Anal fistula	2	9.1
Anal fissure	8	36.4
Anal tags	9	40.9

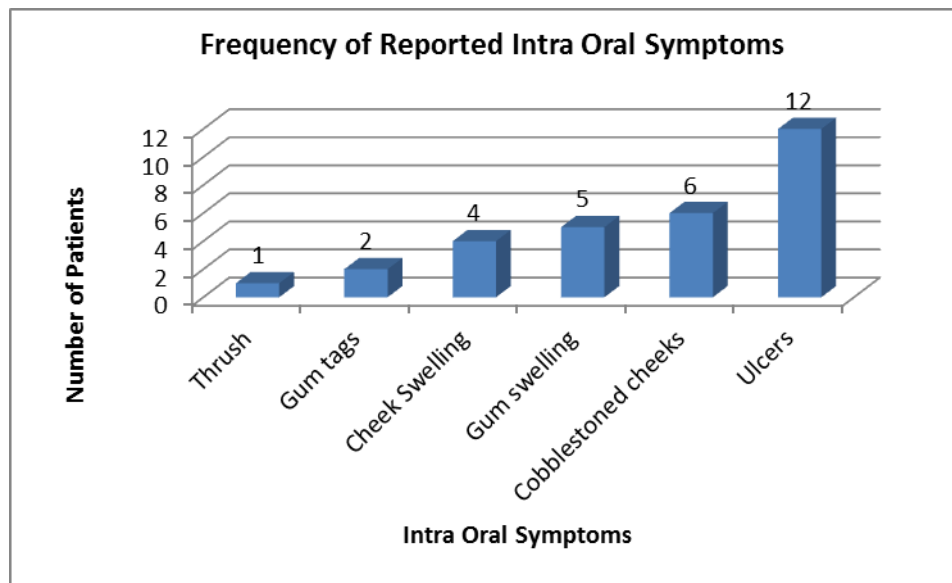
Additional findings included almost two thirds of the patients (n = 14, 63.6%) had been previously diagnosed with eczema. Allergies and food intolerances were found in almost half of the patients (n = 10, 45.5%), while a third had a history of asthma (n = 8, 36.3%). Allergies and food intolerances were found to occur to preservatives, wheat, white rice, chocolate, orange juice, pasta, spices, fatty foods and dairy. These findings do provide some support for the concept of immunological aberration.

Orofacial Manifestations

From the 22 patients assessed, the most commonly reported extra oral symptoms by the patient and parents were fissures and/or cracks in lips (n=12, 54.5%), followed by the corners of the mouth being red, dry and/or cracked (n=9, 40.9%), perioral erythema (n=8,36.4%), swelling of lower lip (n=5, 22.7%), swelling of upper lip (n=4, 18.2%), facial asymmetry (n=2, 9.09%) and eye involvement (n=1, 4.54%). Notably from the patients presenting with swelling of the lips, four out of the five had both swelling of the upper and lower lips. There were no reported cases of facial palsy in this group. (Figure 1)

Figure 1: Frequency of reported extra oral symptoms

The most commonly reported intra oral symptoms were ulcerations (n=12, 54.5%), followed by noticeable lumps and/or cobble-stoning of the cheeks (n=6, 27.3%), gum swelling(s) (n=5, 22.7%), cheek swelling (n=4, 18.2%), gum tags (n=2, 9.09%) and thrush (n=1, 4.54%) (Figure 2). There was variation in the frequency of oral symptoms with 10 patients reporting that it came and went (45.5%), but was persistent for 2 patients (9.09%). It was reported that oral and GI symptoms coincided for only 7 (31.81%) patients, but not for 12 (54.6%) and 3 (13.63%) were not sure. When questioned about the direct relation of oral symptoms to the intensity of CD symptoms, no relationship was reported by 13 (59.1%), but was reported by 6 (27.3%) with the remaining patients (n= 3) not sure about it. A greater association between oral and perianal changes was reported (n=5, 22.7%).

Figure 2: Frequency of reported intra oral symptoms

The mean age for diagnosis of orofacial manifestations was 9 years and 6 months (SD 5.51 years, range, 2.24-14.35 years). Of the 14 patients with oral symptoms, 10 were boys and 4 were girls (5:2). From the extra oral symptoms diagnosed the most common presentation was cheilitis granulomatosa with presentation asymmetrically (n=4), symmetrically (n=2), and presented in the upper (n=1) and lower lip (n=5). The next most common presentation was peri-oral erythema with flaking skin occurring in 4 patients in either a localized (n=3) and generalized (n=1) presentation. Angular cheilitis was only presented bilaterally (n=3) and lip fissuring and/or cracks presented in single (n=1) or multiple (n=2) sites. Facial asymmetry was also diagnosed and found to occur only unilaterally (n= 2) on the right hand side. In contrast chin swelling (n=1) presented on bilaterally. There were no diagnoses of cheek swelling, eye involvement or facial palsy.

The most common intra oral soft tissue diagnosis were gingival swellings (n=10) that were either generalized (n=8) or localized (n=2). Cobblestoned buccal mucosa also presented (n=4) bilaterally (n=3) or unilaterally (n=1). Mucosal and gingival tags were both found to

occur in a single site (n=4, n=2 respectively) and ulcerations (n=2) also presented in a single site. Tongue fissures equally presented in unilateral (n=1) and in multiple sites (n=1). (Table 2)

Table 2: Summary of clinical extra and intra oral findings

Symptoms	Total (n)	
<i>Extra oral</i>		
Cheilitis granulomatosis	Asymmetrical	4
	Symmetrical	2
	Upper lip	2
	Lower lip	5
Peri-oral erythema	4	
Angular cheilitis (bilateral)	3	
Lip fissuring and/or cracks	Single	1
	Multiple	2
Facial asymmetry	1	
Chin swelling	1	
<i>Intra oral</i>		
Gingival swelling	Localised	2
	Generalised	8
Cobblestoned buccal mucosa	Unilateral	1
	Bilateral	3
Tags (single)	Mucosal	4
	Gingival	2
Ulcerations	1	
Tongue fissure	Single	1
	Multiple	1

At the time of clinical assessment more than half of the patients (n = 12, 54.5%) had one type of extra-oral symptom, with 40.9% having two or more extra-oral symptoms. Extra and intra oral symptoms experienced by females were most commonly seen in those above fifteen years of age (n= 3/4) and the distribution of symptoms in males according to age was less common in those below 10 years of age (n=3/10). Of the 3 patients with a total of greater than 5 symptoms (2 males, 1 female) 2 had a slightly higher number of extra oral symptoms. (Table 3)

Table 3: Frequency of extra and intra oral symptoms

Patient	Age (years)	Gender	Total symptoms	Extra Oral symptoms	Intra Oral symptoms
A	6.83	M	8	4	4
B	16.00	M	7	5	3
C	14.92	M	4	2	2
D	6.92	M	3	1	2
E	14.33	M	3	2	1
F	14.50	M	2	0	2
G	13.83	M	2	1	1
H	4.67	M	1	0	1
I	15.50	M	1	0	1
J	10.67	M	1	0	1
K	16.42	F	6	5	1
L	16.25	F	3	1	2
M	9.17	F	3	1	2
N	15.33	F	1	0	1

The role of a dental professional

In the study group, only one third of patients (n = 8 36.4%) patients were under the management of an oral specialist (paediatric dentist n=7, periodontist n=1, and OMFS n=1). The reported treatment for OFG/OCD included topical steroids (n=5), intra-lesional steroids (n=1) and a gingivectomy (n=1). Of patients who were treated for CD, half of the patients reported on an improvement of oral symptoms (n= 11,50%), but it was not evident for 7 (31.8%), and the remainder were unsure about any improvement in oral symptoms(n=4,18.2%). (Table 4)

Table 4: Reported outcome of the oral signs and symptoms following CD therapy

Outcome	N (22)	Percentage %
Improvement	11	50
No improvement	7	31.8
Not sure	4	18.2

When the role of a paediatric dentist in the investigation of CD and OFG was questioned, 18 patients believed that they should be involved (81.8%)

Discussion

It has been documented that over the past 10 years there has been an increasing frequency of incidence of CD in the paediatric population (Phavichitr, Cameron et al. 2003) ESPGHAN (2005), with 20-30% of CD patients being diagnosed before twenty years of age (Phavichitr, Cameron et al. 2003). Retrospective and prospective studies from Europe, Australia and the United States show increased incidence in rates of 0.1 to 4.6 (in the year 2003) over a thirty year period (2005).

The only published Australian data involving children with an IBD in Australia was a retrospective study by Phavichitr *et al.* (2003). Data was collected over a thirty-one year period of children under the age of 16 years old initially diagnosed with CD at the Royal Children's Hospital in Melbourne, Australia. The incidence of CD increased from 0.128/100 000 to 2.0/100 000, with a disproportionate over-representation of children from urban backgrounds (Phavichitr, Cameron et al. 2003). However, no correlation or investigation was made between the incidence and prevalence of OFG and the IBD in this study, resulting in an unknown relationship between OFG and IBD in an Australian paediatric cohort (Phavichitr, Cameron et al. 2003).

In this study the retrospective analysis of the APAIBDD found 945 Australian paediatric patients were diagnosed with CD. The number of paediatric patients diagnosed with Crohn's Disease in South Australia during that time frame was 173 (18.3%), with the mean age of 12.8 years at the time of diagnosis of Crohn's Disease (SD 3.6, range 1.1-24.2 years) in South Australia. From this data alone it is not possible to determine if there have been any changes to the incidence of paediatric CD or OFG.

The APAIBDD data consisted of 109 males (109/173, 63.0%) with a mean age of 12.6 years (SD 3.8, range 1.1-24.2 years) and 65 females (65/173, 37.6%) with a mean age of 13.2 years (SD 3.2, range 3.4-19.2 years). These mean ages are higher than those previously reported at 10.1 (Pfefferkorn, Burke et al. 2009) to 10.3 (Heyman, Kirschner et al. 2005) years of age. This Australian data also supports other reports that there is a greater incidence of CD in males (Sauer and Kugathasan 2009), described as being 54% (Heyman, Kirschner et al. 2005) to 65 % (Pfefferkorn, Burke et al. 2009).

Further analysis of the APAIBDD found that nationally, 8.6% of paediatric CD patients have oral manifestations (81/945), while in South Australia, 9.3% of paediatric patients diagnosed with CD were recorded as having had oral manifestations (16/173) at the time of their gastroenterological consultation.

In this study, clinical assessment by a dentist found that there were oral signs in 63.6% (n=14) of this cohort of South Australian paediatric patients. These results are closer to findings in an Irish paediatric population where 45-48% had oral symptoms diagnosed by gastroenterologists (Pittock, Drumm et al. 2001; Harty, Fleming et al. 2005). These results are in keeping with the reported extra and intra oral symptoms occurring prior to and at the time of GI consultation (n=12, 54.5%) in this study.

The difference in diagnosis of oral symptoms in South Australian patients is supported by findings by Harty *et al.* (2005) where there was a difference in oral findings recorded by

gastroenterologists and the dentist with the former group failing to identify 55% (n=11) of oral lesions(Harty, Fleming et al. 2005). As the APAIBDD data is entered by the gastroenterologists there is the potential that the oral symptoms are under reported.

The presentation of oral manifestations at the time of assessment may be reduced by the concurrent therapy for CD. Future directions for research could involve a detailed assessment of the type and dose of therapy received in relation to the GI and orofacial clinical signs and symptoms. Additionally, the PDU and Department of Gastroenterology established a protocol so that children with suspected CD are referred to the PDU for investigation prior to the use of systemic medications. Analysis of the clinical findings arising from this process could gain further insight into the orofacial manifestations of non-medicated paediatric CD patients.

The involvement of paediatric dentists in the investigation of paediatric patients with suspected OFG and other orofacial manifestations could lead to an early diagnosis of CD and improvement of the patient's health outcome through decreasing long term permanent systemic manifestations. Recognition and diagnosis of active systemic disease such as CD would result in earlier management and remission of the disease (Phavichitr, Cameron et al. 2003), and improve long term prognosis and decreased the potential problems affecting the daily function and quality of life for the patient, their family and the burden of chronic disease on the public health system that may result from poorly controlled CD. Although 18 of the 22 patients believed that a paediatric dentist should be involved in the investigative process, there is potential bias due to the background of the researchers involved.. Future research could involve detailed assessment of the patient's past dental history including their

frequency of attendance for dental reviews, past dental treatment and if they experienced any changes in their quality of life following treatment.

Extra-intestinal findings may present without significant intestinal symptoms (Freeman 2004) and may manifest in 25-30% of CD patients (Ulnick and Perkins 2001). There may be orofacial signs and symptoms (Table 5), ocular manifestations, as well as arthritis, liver and renal manifestations (Ploysangam, Heubi et al. 1997; Tonkovic-Capin, Galbraith et al. 2006).

Table 5. Summary of clinical features of OFG and OCD

<i>Extra Oral Manifestations</i>	<i>Intra Oral Manifestations</i>	<i>Neurological Manifestations</i>
Periorbital swelling	Lingua fissures	Facial palsy
Eyelid swelling	Mucosal tags	
Swelling of the zygomatic region	Cobblestoned mucosa	
Chin swelling	Gingival tags	
Cheilitis granulomatosis	Granulomatous gingiva	
Angular cheilitis	Ulceration	
Cervical lymphadenopathy	Median cheilitis	
Facial erythema		
Lip swelling		
Lip Fissuring		

In this study a range of triggers intensifying oral signs and symptoms were reported, with identification that specific foods consumed were the most common trigger i.e. chocolate, salty foods, potato chips and tomatoes. Other identified triggers included toothpaste (n=2) and mouthwash (n=1). These findings are consistent with published findings that have indicated that OFG may result from hypersensitivity reactions to food and food preservatives (Wray, Rees et al. 2000; Tilakaratne, Freysdottir et al. 2008). Patients with OFG are more likely to react to food additives especially benzoic acid, a commonly used food preservative also found in cosmetics, dyes and plastics.

A variety of food products have been identified as causing food hypersensitivity in OFG patients. These products include wheat, dairy products, chocolates (Wray, Rees et al. 2000), eggs, peanuts, cinnamaldehyde, carbonyl piperitone, cocoa, carvone, carmoisine, sunset yellow dye and monosodium glutamate (MSG) (Sweatman, Tasker et al. 1986; Sciubba and Said-Al-Naief 2003). A common material which may affect OFG patients is tooth paste which contains cinnamaldehyde or carbonyl piperitone (Sweatman, Tasker et al. 1986).

The mean age for diagnosis of orofacial symptoms in this study was 9 years and 6 months (SD 5.51 years, range, 2.24-14.35 years). Currently there is no published data about the incidence and prevalence of OFG or OCD in an Australian adult or paediatric population. Of the 14 patients with oral symptoms (63.6%), 10 were boys and 4 were girls (5:2). These findings are in keeping with those by Harty et al. (2005) who also found a greater incidence in boys than girls (1.5:1)(Harty, Fleming et al. 2005).

At the time of clinical assessment more than half of the patients (n = 12, 54.5%) had one type of extra-oral symptom, with 40.9% having two or more extra-oral symptoms. These findings are similar to those by Harty et al. (2005) who also reported that more than half the patients had more than 1 type of oral lesions(Harty, Fleming et al. 2005).

As part of routine CD investigations, laboratory studies conducted (Walker-Smith 1994; Sathiyasekaran and Shivbalan 2006; Wu. G 2010) may indicate the presence of inflammatory activity or nutritional deficiencies (Grossman. A 2009; Wu. G 2010). Active CD activity can be also be assessed by the levels of acute inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) that can specifically evaluate Crohn's colitis (Lecis, Germana et al. 2002; Wu. G 2010).

Specific serological tests for identification of CD activity involve assessment of the presence *anti-Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear-staining antineutrophil cytoplasmic antibodies (p-ANCA) (Wu, G 2010). Increases in ASCA have been reported in up to 60% of CD patients (Vermeire, Van Assche et al. 2004). Russell *et al.* (2009) investigated the role of *anti-Saccharomyces cerevisiae* antibodies (ASCA) status and its relation to disease phenotypes in patients with IBD (Russell, Ip et al. 2009). Tests positive for ASCA and negative for p-ANCA suggests the presence of CD compared to UC and healthy controls (Russell, Ip et al. 2009; Wu, G 2010). A positive ASCA was also associated with OCD, perianal CD, presence of granulomata and markers of disease severity (Russell, Ip et al. 2009).

The activity of CD in this study was assessed according to the serological results and correlated with the clinical OFG/OCD activity scores. As there is not a recognized system for assessing the severity of OFG/OCD, the OFG/Oral manifestations disease activity index was devised by the researchers. The scoring system was based on the 'Paediatric Crohn's Disease Activity Index scoring system' that is internationally used to indicate disease activity. Currently there is no literature on OFG/OCD based on serological results and clinical activity. Although there has been data about the symptoms and oral sites involved in OFG/OCD in paediatric patients (Pittock, Drumm et al. 2001) the severity of the condition has not been assessed.

Potential outcomes of this pilot study would be the analysis and publication of data specific to an Australian Paediatric population in regards to the incidence and prevalence of OFG and other oral involvement with or without CD. The significance of the presence of oral signs and

symptoms can be established and correlated with the incidence of active CD. From the research, the clinical images obtained were used to develop a visual guide. Further research can be conducted to assess the efficiency of the activity index and visual guide in disease diagnosis and assessment of severity. Potentially they could be used to determine the prevalence and severity of OFG and other oral involvement by dental, non-dental and non-oral physicians. This could then lead to earlier and more accurate diagnosis of all signs and symptoms, and management of the disease.

Conclusion

In a South Australian paediatric population there is a high incidence of oral symptoms presenting in patients with CD. From the results obtained, there is Assessment of oral symptoms using an OFG/oral activity score and visual guide may aid diagnosis and assessment of the disease severity by attending gastroenterologists and dentists.

Chapter IV

Article 2 (Scientific Article)

A comparison of the histopathological features of oral and gastrointestinal lesions in patients with Crohn's disease and/or orofacial granulomatosis

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Abstract

Background: There is debate about the relationship between orofacial granulomatosis and Crohn's disease. This study was a pilot investigation to establish if there are clinical and histological similarities between OFG and CD.

Methods: A retrospective analysis of oral and gastrointestinal biopsies from 8 paediatric patients who had had a provisional diagnosis of OFG and for which subsequent investigation for CD was undertaken. The histopathological features of oral and gastrointestinal lesions in each patient were compared.

Results: Granulomas were seen in all buccal mucosa and mandibular anterior labial mucosa biopsies, 3 (n=5) of the lower lip specimens and 2 (n=4) of the attached gingival biopsies. Of the 8 patients assessed, 6 were diagnosed with OFG on the basis of the oral biopsies. Only 1 patient had both macroscopic and microscopic changes consistent with active Crohn's disease. In addition, all 6 patients with OFG had perianal disease. A multidisciplinary approach to investigating all relevant clinical, histological and serological information resulted in 7 of the 8 patients having a final diagnosis of CD.

Conclusion: There is no conclusive evidence found linking OFG and Crohn's disease, however given the strong association between the two conditions and other clinical and serological markers, multidisciplinary management is recommended to establish a definitive diagnosis.

Introduction

Orofacial granulomatosis (OFG) is the term given to describe noncaseating granulomatous disorders and lymphoedema involving oral and maxillofacial soft tissues (Wiesenfeld, Ferguson et al. 1985; Leao, Hodgson et al. 2004). OFG encompasses characteristics of oral Crohn's disease (OCD), oral sarcoidosis, Melkersson Rosenthal syndrome (MRS) and cheilitis granulomatosa (CG) of Miescher (Tilakaratne, Freysdottir et al. 2008). Numerous disorders may present with persistent and/or recurrent labial enlargement and intraoral swellings that have a similar histopathological feature of noncaseating granulomas (Bogenrieder, Rogler et al. 2003; Leao, Hodgson et al. 2004). Varying incidences have been reported of the presence of oral lesions associated with Crohn's disease (CD) and with ulcerative colitis (UC) (Pittock, Drumm et al. 2001; Harty, Fleming et al. 2005).

Investigations of OFG include clinical, haematological, radiographic and histopathological examinations to ensure a correct diagnosis. The diagnostic criteria for OFG and CD are presented in Table 1. Debate exists regarding nomenclature and the link between CD and OFG based on the similarities in underlying immunological mechanisms (Satsangi and Jewell 1994; Gibson, Wray et al. 2000; Tilakaratne, Freysdottir et al. 2008).

Table 1: Summary of the current clinical and histopathological diagnostic criteria for OFG and CD

Clinical features	OFG	CD
	Recurrent orofacial swelling	Any site along the GI tract
	Involve atypical sites	Intra Intestinal features
	<ul style="list-style-type: none"> - One or both lips - Chin - Cheeks - Peri-orbital area - Zygomatic tissues - Lymph nodes 	<ul style="list-style-type: none"> - Abdominal pain - Diarrhoea - Weight loss - Constipation - Melena

- Eyelids
- Forehead

Extra Intestinal features

Condition

- Cheilitis granulomatosis
- Peri-oral erythema
- Angular cheilitis
- Median cheilitis
- Mucosal swelling (cobblestoned appearance)
- Mucosal tags
- Granulomatous gingiva
- Lingua fissures
- Facial nerve palsy
- Facial swelling
- Cervical lymphadenopathy
- Ulcers (linear)

- Peri-anal disease
- Fever
- Fatigue
- Anorexia
- Diminution of growth velocity
- Skin manifestations
- Ocular
- Arthritis
- Bone disease
- Liver and renal manifestations
- Orofacial

Recurrent swelling involving atypical sites

Cheilitis granulomatosis

Peri-oral erythema

Angular cheilitis

Median cheilitis

Mucosal swelling (cobblestoned appearance)

Mucosal tags

Granulomatous gingiva

Lingua fissures

Ulcers (linear)

Histological features

- Noncaseating & epithelioid granulomas with or without multi-nucleated giant cells
- Oedema
- Lymphoedema
- Lymphangiectasia
- Perivascular lymphocytic infiltration
- Noncaseating & epithelioid granulomas with or without multi-nucleated giant cells
- Aphthoid ulcers
- Fissure ulcers
- Transmural inflammation
- Lymphangiectasia
- Fibrous structuring
- Neural changes
- Chronic inflammation

The aim of this pilot study was to investigate if there is a histopathologic relationship between OFG and CD. Understanding any relationship between the two conditions has important clinical implications, for example if OFG is a precursor to, or an early stage manifestation of CD in a paediatric population, its identification could aid in diagnosis, and to enable early clinical management of the disease (Bogenrieder, Rogler et al. 2003; Tilakaratne, Freysdottir et al. 2008; Rowland, Fleming et al. 2009).

Materials & Methods

A retrospective assessment was conducted on biopsy specimens obtained from South Australian paediatric patients as part of their wider investigations for OFG and/or CD. The patients were selected from the Oral Biopsy Database in the Department of Pathology, Women's and Children's Hospital (WCH). This database was commenced in 2003, and all records obtained between 2003 and 2009 were analysed in this study.

Oral biopsies

All biopsies were undertaken by an Oral and Maxillofacial Surgeon or Paediatric Dentistry Consultant under general anaesthesia. The deep incisional biopsy technique was used to obtain all specimens that was stored in formalin solution . The oral biopsy sites were chosen according to the presence of clinically obvious lesions in the mouth.

Gastrointestinal biopsies

All gastrointestinal biopsies were undertaken by a Paediatric Gastroenterologist under general anaesthesia.

The specimens were processed in the Department of Pathology (WCH) and stained with haematoxylin and eosin (H & E). Histopathological assessment of the biopsy specimens was undertaken by Pathologists at the WCH or the Institute of Medical and Veterinary Science (IMVS) (now SA Pathology).

Results

Oral lesions

The Paediatric Dentistry and Pathology Departments of the WCH had records of 8 South Australian paediatric patients who were investigated for OFG with or without CD. These specimens were collected over a period of 6 years. One patient underwent 2 oral biopsies. The mean age of the patients at the time of biopsy was 10.8 years (SD \pm 4.4); 7 of the 8 patients were male.

Granulomas were seen in all buccal mucosa (Figure 1) and mandibular anterior labial mucosa biopsies, 3 out of 5 of the lower lip specimens (Figure 2) and 2 out of 4 of the attached gingival biopsies (Table 2). The presence of granulomas was consistent with the diagnosis of OFG. The histological features of the oral and GI lesions from each patient are summarized in Table 3, (See Appendices X and XI for greater detail).

Figure 1. Buccal mucosa biopsy specimen showing dermal infiltration, dense inflammatory cells and scattered granulomata

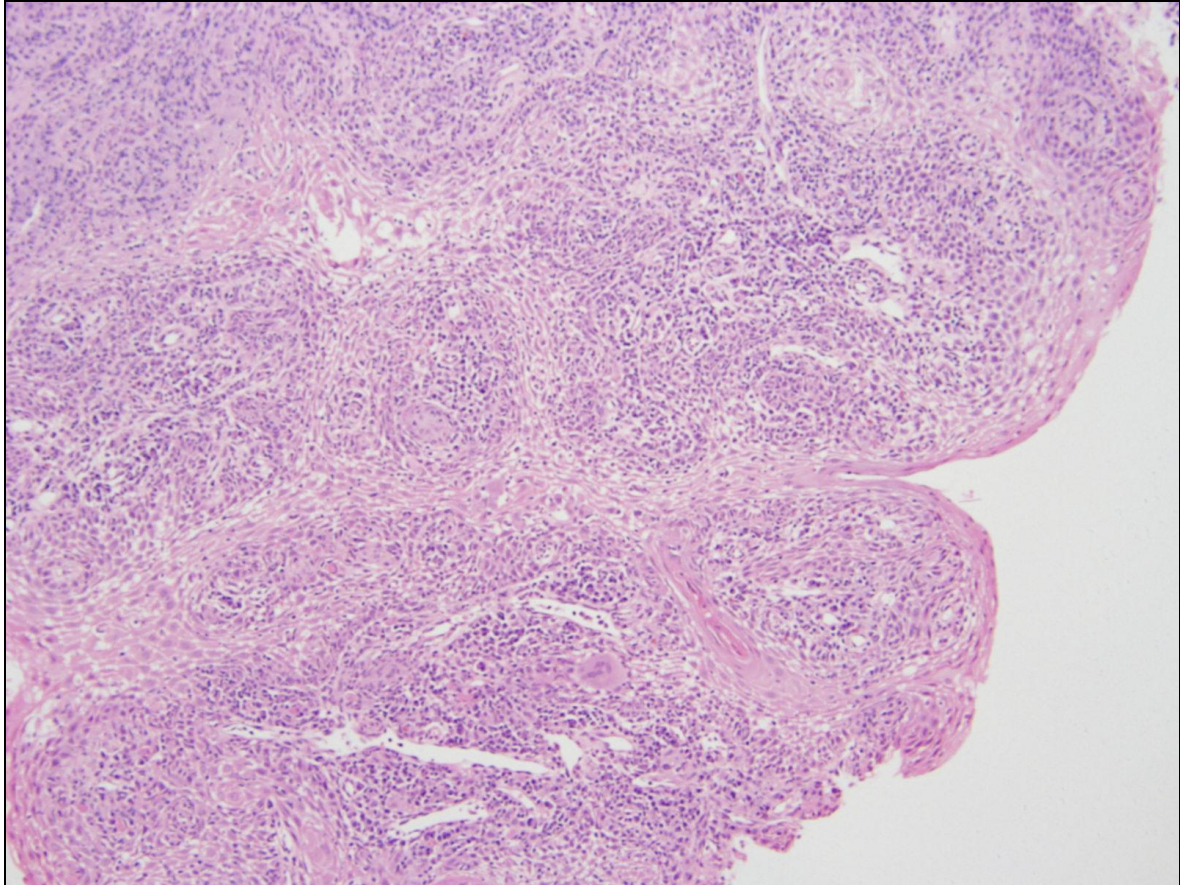


Figure 2. Lower lip biopsy specimen showing dermal infiltration with multinucleated giant cells and scattered granulomata

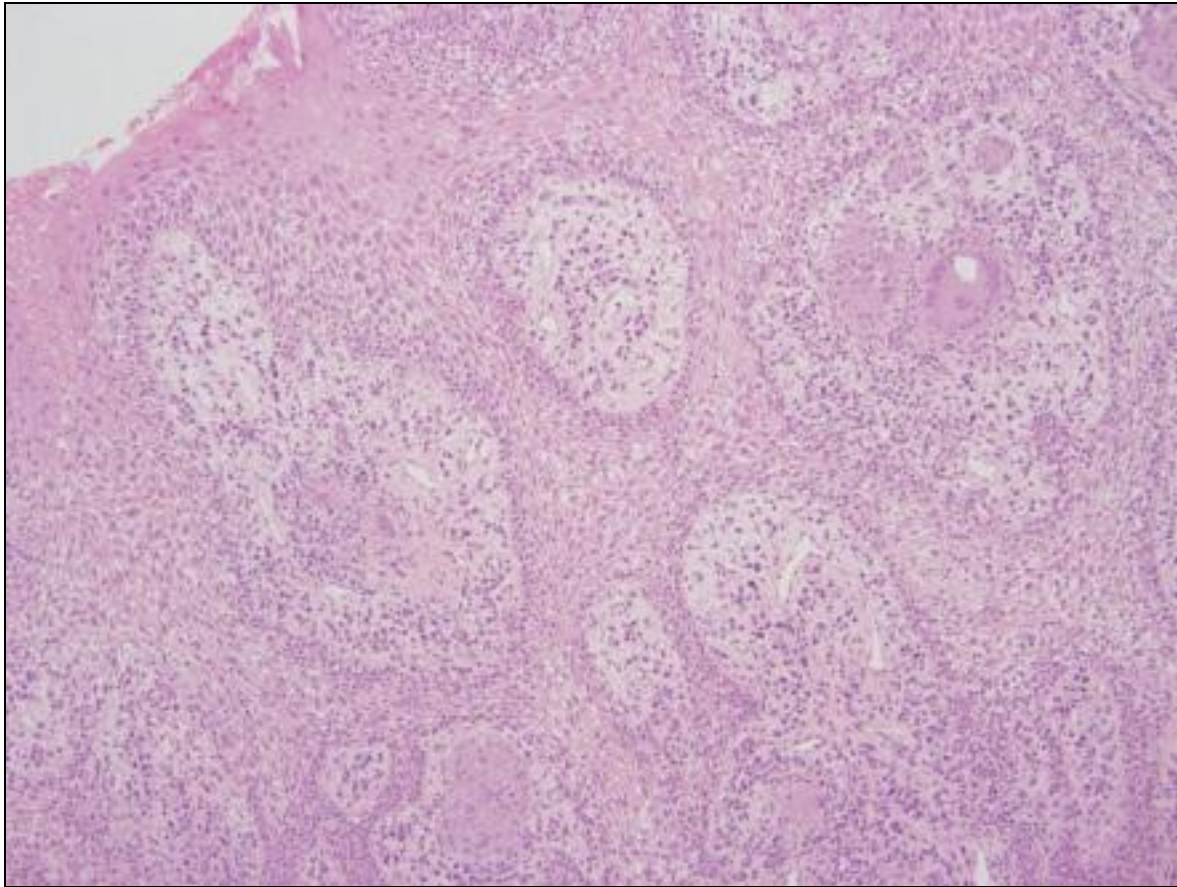


Table 2. Summary of sites diagnosed as OFG

SITES	OFG
Cheek	4 (n=4)
Lower Lip	3 (n=5)
Mandibular anterior labial mucosa	2 (n=2)
Gingiva	1 (n=2)

Comparison between oral and gastrointestinal histological findings

From the 8 oral biopsy specimens assessed, OFG was histologically diagnosed in 6 cases. Of the patients with OFG, 2 did not have any other GI pathology, 1 had mild oesophagitis and no GI pathology, 1 had mild duodenal colitis and no other GI pathology, and 1 had mild oesophagitis, gastric antrum granulomata and duodenal mild inflammation. Only 1 OFG patient had pathology that extended throughout the GI tract and was the only patient with histological perianal granulomas. (Table 3)

Table 3: Summary of oral and GI diagnosis (histological)

Patient	A	B	C	D	E	F	G	H
Oral	Granulomatous inflammation	Mild non-specific inflammatory changes	Granulomatous inflammation	Granulomatous inflammation	Granulomatous inflammation	Chronic sialadenitis	Granulomatous inflammation	Granulomatous inflammation
Oesophagus	Normal	Mild non-specific oesophagitis	Moderate oesophagitis	Mild oesophagitis	Mild oesophagitis	Normal	Normal	Normal
Gastric Antrum	Normal	Chronic inflammation	Mild gastritis with mucosal ulceration	Granulomata	Normal	Normal	Normal	Normal
Duodenum	Mild colitis	Normal	Normal	Mild inflammation	Normal	Normal	Normal	Normal
Terminal ileum	Normal	Normal	Mucosal granuloma	n/a	Normal	Normal	Normal	Normal
Caecum	Normal	Normal	Mild chronic colitis with mucosal granulomas	n/a	Normal	n/a	Normal	Normal
Hepatic flexure	n/a	n/a	Mild chronic colitis	n/a	n/a	Chronic colitis	Normal	Normal
Transverse colon	n/a	n/a	n/a	n/a	n/a	Chronic colitis	Normal	Normal
Rectal-sigmoid colon	n/a	Normal	Mild chronic colitis with mucosal granulomas	n/a	Normal	Granulation tissue	Normal	Non-specific inflammation
Rectum	n/a	n/a	Chronic proctitis with mucosal granulomas	n/a	n/a	Mild colitis	n/a	normal

Comparison between oral and gastrointestinal clinical findings

At the time of biopsy collection, a brief clinical summary of symptoms was provided with the biopsy specimen to aid in the differential diagnosis for the pathologist. Of the 7 cases of cheilitis granulomatosis (CG) there were 6 presenting with clinical perianal disease (Table 4).

Table 4. Reported orofacial and GI clinical summary

Patient	Orofacial Symptoms	Gastrointestinal Symptoms
A	Cheilitis granulomatosis	Perianal disease
B	Cheilitis granulomatosis	Perianal disease
C	Cheilitis granulomatosis	Oesophageal involvement Perianal disease Crohn's colitis
D	Cheilitis granulomatosis Cobblestone buccal mucosa	n/a
E	Cheilitis granulomatosis Cobblestone buccal mucosa	Weight loss
F	Ulceration	Perianal disease Weight loss
G	Cheilitis granulomatosis Sore mouth	Colitis Perianal disease
H	Cheilitis granulomatosis OFG	Perianal disease

Comparison between gastrointestinal histological and clinical findings

Although only 2 patients had histological GI granulomas, 7 of the 8 patients were diagnosed with CD by their Paediatric Gastroenterologist based on their clinical symptoms, serology and oral and gastrointestinal microscopic findings (Table 5).

Table 5: Summary of oral and gastrointestinal diagnosis based on combined clinical, serological and histological findings

Patient	Oral Diagnosis	GI diagnosis
A	OFG	CD
B	Non-specific inflammatory changes	No CD
C	OFG	CD
D	OFG	CD
E	OFG	CD
F	Scarring, inflamed salivary glands Chronic sialadenitis	CD
G	OFG	CD
H	Mild inflammation OFG	CD

Discussion

This study found that of the 8 South Australian paediatric patients investigated for OFG and/or CD 7 were diagnosed with CD and 6 were diagnosed with OFG. The retrospective analysis was to investigate potential clinical and histological links between OFG and CD. This shows that thorough oral and gastrointestinal investigations should be conducted. Debate exists in general surgical and dental literature regarding the extent to which a patient presenting with OFG should be investigated for chronic granulomatous disease elsewhere (Field and Allan 2003). Multi-disciplinary management involves input from gastroenterologists, dermatologists, general medical practitioners, dieticians, oral and maxillofacial surgeons and dentists will lead to the best outcome for the patient (Field and Allan 2003) including a higher rate of definitive diagnosis and therefore a higher rate of definitive treatment.

Diagnosis of OFG in patients is based on the clinical presentation of recurrent orofacial swellings (Grave, McCullough et al. 2009) and confirmed by histological findings (Mignogna, Fedele et al. 2001; Mignogna, Fedele et al. 2003). Despite the variable

presentation of OFG, it can be differentially diagnosed based on clinical presentation (Leao, Hodgson et al. 2004). The oral sites involved in this study are consistent with that reported in the literature. The most commonly affected areas are the lips, labial and/or buccal mucosa, or gingiva (Field and Allan 2003).

Histologically, the presence of granulomata is diagnostic for OFG, but not mandatory as diagnosis can be established from the patient's history and clinical features alone (Scully, Cochran et al. 1982; Wiesenfeld, Ferguson et al. 1985; van der Waal, Schulten et al. 2002; Leao, Hodgson et al. 2004). It was reported by Sanderson *et al.* (2005) that 68-100% of OFG biopsy specimens show noncaseating and epithelioid granulomas with or without multinucleated giant cells (Sanderson, Nunes et al. 2005). In this study, 75% of patients had granulomatous lesions identified in the biopsies.

Furthermore, the histological features of oedema, lymphangiectasia, and perivascular lymphocytic infiltration were also found in the patients in this study, which was consistent with the findings reported by Wiesenfeld et al. (1985). However, unlike that previous report (Wiesenfeld, Ferguson et al. 1985), no lymphoedema was reported in the patients in the present study.

From the 8 oral biopsy specimens assessed OFG was histologically diagnosed in 6 cases. Of the patients with OFG, only one patient had pathology extending throughout the GI tract and was the only patient with histological perianal granulomas. These results are consistent with reports by Freeman (2004) that extra-intestinal findings may present without significant intestinal symptoms (Freeman 2004) and may manifest in 25-30% of CD patients (Ulnick and Perkins 2001).

Extra-intestinal manifestations of CD include orofacial signs and symptoms, perianal disease, ocular manifestations, as well as arthritis, liver and renal manifestations (Ploysangam, Heubi et al. 1997; Tonkovic-Capin, Galbraith et al. 2006). Perianal disease may present with abscess formation, perirectal and perianal fistulisation, and may precede intestinal manifestation by years (Singh, Mc et al. 2004). Vernie Massouille *et al.* (2008) found that 9% of paediatric patients had perianal disease (abscesses or fistulae) at diagnosis and 27% when followed up 7 years later (Vernier-Massouille, Balde et al. 2008). When assessing the reported oral and GI clinical symptoms at the time of biopsy, it was found that 6 of the 8 patients (75%) experienced perianal disease.

In the diagnosis of CD comprehensive gastrointestinal assessment involves detailed history taking, physical examination, and a range of investigations (Sathiyasekaran and Shivbalan 2006). Investigations include laboratory studies, imaging studies and procedures (Walker-Smith 1994; Sathiyasekaran and Shivbalan 2006; Wu. G 2010). Laboratory studies may indicate the presence of inflammatory activity or nutritional deficiencies (Grossman. A 2009; Wu. G 2010). Active CD activity can be also be assessed by the levels of acute inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) that can specifically evaluate Crohn's colitis (Lecis, Germana et al. 2002; Wu. G 2010). Endoscopies and colonoscopies are invaluable and considered a standard procedure in CD investigation (Grossman. A 2009), performed for assessment of CD activity and disease complications (Sathiyasekaran and Shivbalan 2006). They are used to obtain biopsies for histopathological assessment (Wu. G 2010). The rate of granuloma detection in intestinal lesions has been reported to be as high as 71% (Plauth, Jenss et al. 1991).

The investigation of oral CD is the same as that for OFG. Recommendations for systematic examination by clinicians experienced with oral pathology for greater accuracy in identification of lesions presenting with CD. Harty *et al.* (2005) and Pittock *et al.* (2001) found that less than 50% of children with disease-specific lesions were accurately identified by gastroenterologists (Pittock, Drumm *et al.* 2001; Harty, Fleming *et al.* 2005). They recommended that in addition to the routine laboratory and imaging studies, there should be systematic clinical assessment of the oral cavity including the submandibular lymph nodes, lips, labial mucosa and sulci, commissures, buccal mucosa and sulci, gingival, tongue, floor of mouth, and hard and soft palate (Pittock, Drumm *et al.* 2001; Harty, Fleming *et al.* 2005). Oral biopsy specimens should be taken when clinically indicated (Harty, Fleming *et al.* 2005). Oral lesions are ideal sites for initial investigation for CD as oral lesions commonly contain granulomas (71%) (Plauth, Jenss *et al.* 1991) and are easily accessible for diagnostic biopsies (Harty, Fleming *et al.* 2005). Future research could involve additional immunohistochemistry assessment of the biopsy specimens.

The findings from this study are in keeping with earlier reports that children have a higher expression of the initial manifestation of CD by oral lesions (OCD) which may occur years ahead of intestinal symptoms (Khouri, Bohane *et al.* 2005). Not all clinical features of OFG are present in every patient, with a wide range in individual variations in the signs and symptoms that present (Ghandour and Issa 1991; Dummer, Lurz *et al.* 1999). It has been reported that the onset of oral symptoms occurs at a younger age (Dupuy, Cosnes *et al.* 1999). Onset of oral lesions may precede (Plauth, Jenss *et al.* 1991) or establish at any time during the intestinal disease (Basu and Asquith 1980; Scully, Cochran *et al.* 1982; Harty, Fleming *et*

al. 2005). Pittock *et al.* (2001) also found that children with OCD at the time of examination were more likely to have macroscopic and microscopic disease proximally in the GI tract(Pittock, Drumm et al. 2001).

Conclusion

OFG may occur with or without any microscopic changes in the gastrointestinal tract. There was no conclusive evidence found linking OFG and Crohn's disease, however given the strong association between the two conditions, and other clinical and serological markers, multidisciplinary management is recommended to establish a definitive diagnosis. For patients diagnosed with OFG with serological evidence of Crohn's disease should be monitored for the onset of GI symptoms.

Chapter V.
Article 3 (Case Report)

Is Orofacial granulomatosis a precursor to paediatric Crohn's disease?

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Abstract

It has been suggested that orofacial granulomatosis (OFG) may be a precursor to, or an early stage manifestation of Crohn's disease (CD) in a paediatric population. These case reports describe two young boys who were initially referred to the Department of Paediatric Dentistry with oral signs and symptoms of orofacial granulomatosis. These case reports also outline initial symptoms, investigations and treatment, and highlight the need for multidisciplinary management in these cases. The possible link between orofacial granulomatosis and Crohn's disease is discussed.

Key Words: OFG = orofacial granulomatosis, CD = Crohn's disease, OCD= oral Crohn's disease

Introduction

Orofacial granulomatosis (OFG) is the term given to describe noncaseating granulomatous disorders and lymphoedema involving oral and maxillofacial soft tissues (Wiesenfeld, Ferguson et al. 1985; Leao, Hodgson et al. 2004). It is considered to be an uncommon disorder (Leao, Hodgson et al. 2004) with increasing recognition and debate regarding associated nomenclature, as well as implications and relation to other disease processes (Tilakaratne, Freysdottir et al. 2008).

OFG encompasses characteristics of oral Crohn's disease (OCD), oral sarcoidosis, Melkersson Rosenthal syndrome (MRS) and cheilitis granulomatosa (CG) of Miescher (Tilakaratne, Freysdottir et al. 2008). Numerous disorders may present with persistent and/or recurrent labial enlargement and intra oral swellings that have a similar histopathological feature of noncaseating granulomas (Bogenrieder, Rogler et al. 2003; Leao, Hodgson et al.

2004). Therefore it is important that a correct diagnosis is established in order to facilitate prompt and appropriate systemic therapy to manage the associated signs and symptoms and systemic manifestations of the disease (Leao, Hodgson et al. 2004; Rowland, Fleming et al. 2009). Early diagnosis may also lead to reduction or prevention of significant cosmetic orofacial problems, and avoid the condition progressing to the development of systemic OFG-related diseases (Mignogna, Fedele et al. 2003).

This case report presents two cases which exhibit the features of OFG and CD.

Patient 1

A 27-month-old boy of indigenous descent was referred to the Department of Paediatric Dentistry by a Paediatric Immunologist regarding a history of upper lip swelling and bilateral cervical lymphadenopathy. His past medical history included bronchiolitis at 8 months of age, recurrent ear infections, mild eczema and asthma. His medical history was otherwise unremarkable and there was no family history of inflammatory bowel disease.

Patient 1 first developed facial angioedema at 21 months of age that fluctuated in severity over a 6 month period. At 24 months he was admitted due to marked facial swelling and extensive cervical lymphadenopathy. A concomitant rash would develop on his cheeks when there was upper lip swelling. There were no reported precipitating factors or changes to his oral intake. Initial investigations had not provided a diagnosis.

Patient 1 was initially seen by a paediatric dentist 6 months after his first symptoms. Initial examination revealed bilateral regional lymphadenopathy in the submandibular and superior cervical nodes. There was significant enlargement of the upper lip with widespread fissuring

and perioral erythema. The lips were firm to palpate and small erythematous lesions of 1-2mm diameter were present on his cheeks. Intra-oral examination revealed the patient was in the full primary dentition stage with no caries or dental anomalies present. The maxillary and mandibular anterior labial mucosa was erythematous with an atypical appearance, while the buccal mucosa exhibited a distinct cobblestone appearance. No ulcerations were present at the time of examination. (Figures 1a, 1b)

Figure 1a: Patient 1- Facial view of the swelling of the upper lip with fissuring and perioral erythema



A multi-disciplinary approach involving a Paediatric Immunologist, Paediatric Dentist and a Paediatric Gastroenterologist was coordinated to investigate his clinical signs and symptoms. Initial serology investigation indicated a positive ASCA and negative p-ANCA result,

favouring diagnosis of CD. All other testing was otherwise non-diagnostic for any other conditions.

Figure 1b: Patient 1- intra oral view of the mandibular labial granulomatous gingiva

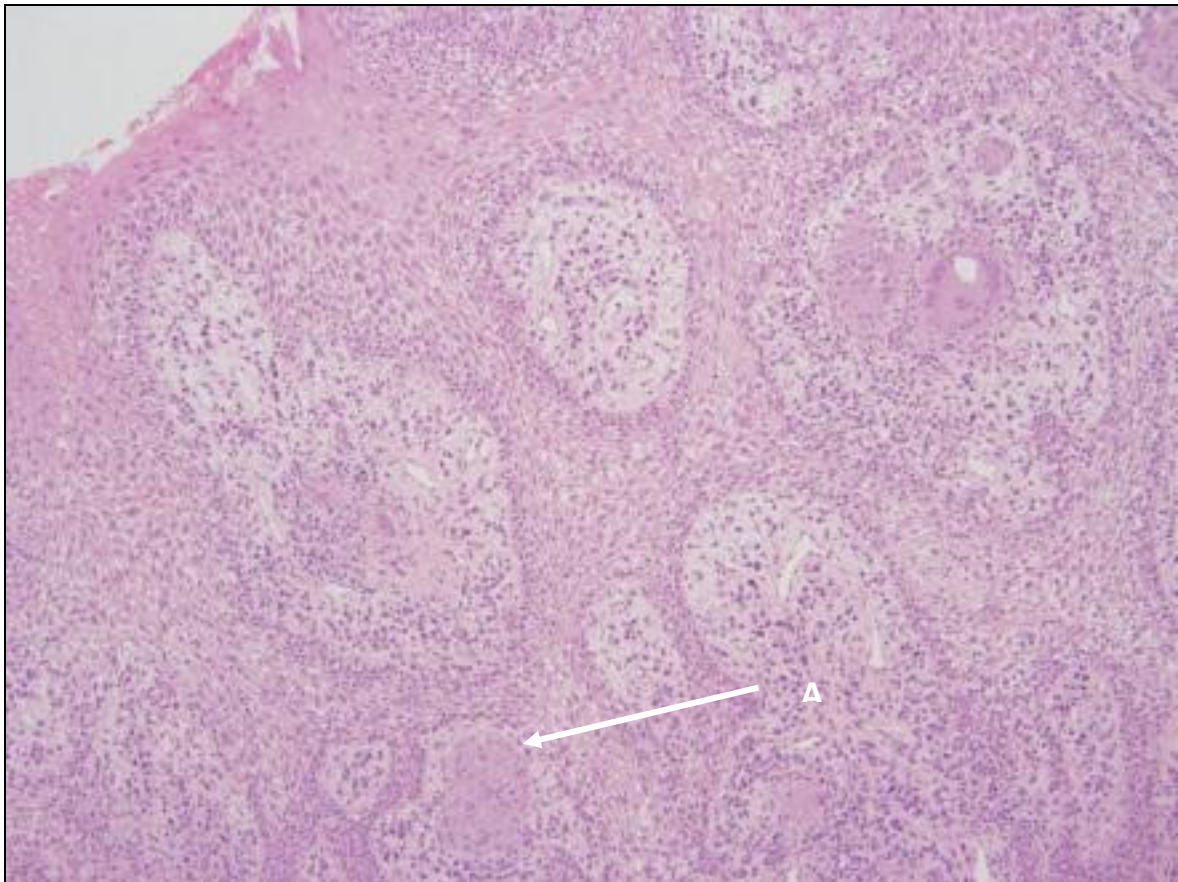


Under general anaesthesia oral biopsies of the upper lip and left buccal mucosa were taken by the paediatric dentist, and upper endoscopy and colonoscopy was performed by a paediatric gastroenterologist. Histological assessment found that both oral specimens showed non-keratinizing squamous epithelium with underlying dermis, patchy widespread dermal infiltration that included epithelioid histiocytes, multinucleated giant cells and scattered formed granulomata admixed with lymphocytes, plasma cells and eosinophils. (Figures 2a, 2b) These findings were consistent with the clinical diagnosis of OFG. The upper and lower

gastrointestinal biopsies featured mild inflammation in the oesophagus and terminal ileum.

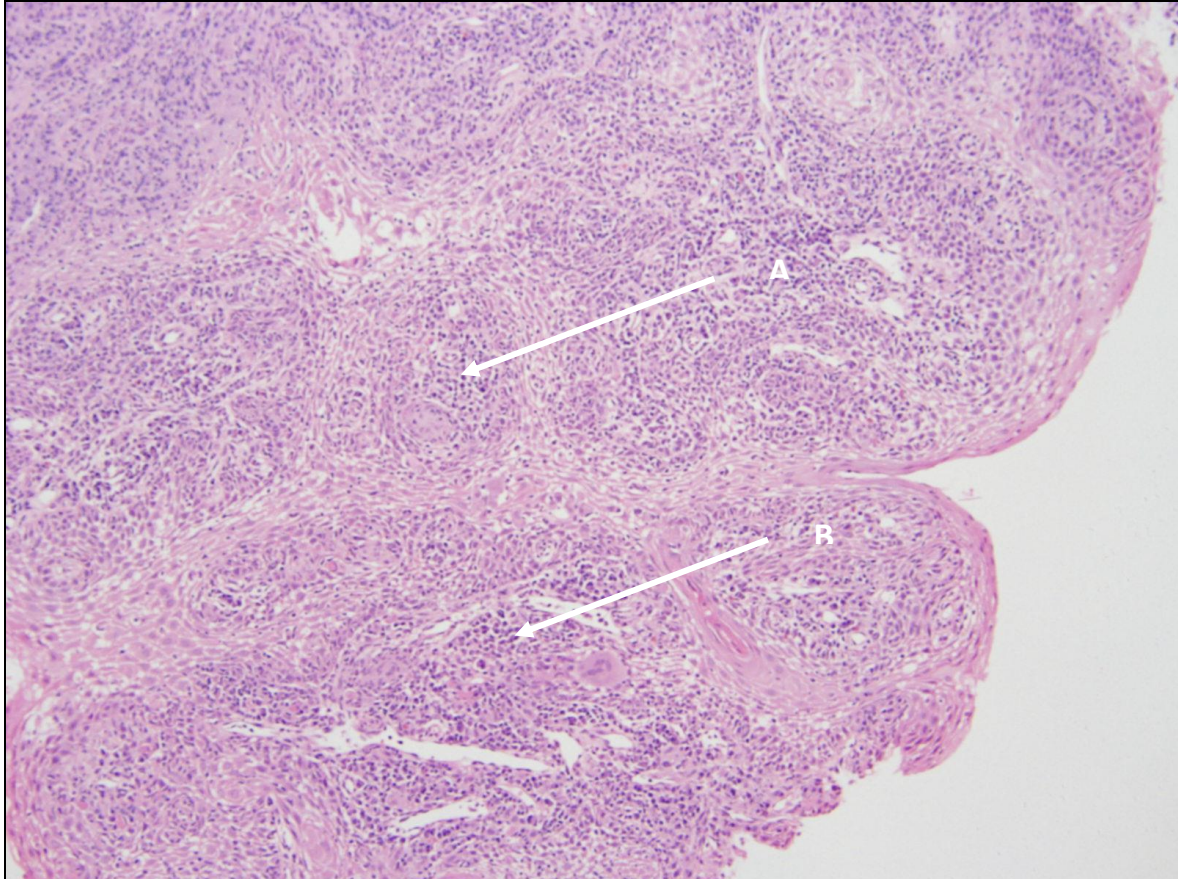
There was also no sign of peri-anal disease.

Figure 2a. Lower lip biopsy specimen viewed at x10 magnification showing dermal infiltration with multinucleated giant cells and scattered granulomata



A= Granulomata

Figure 2b. Buccal mucosa biopsy specimen viewed at x20 magnification showing dermal infiltration, dense inflammatory cells and scattered granulomata.



A= Granulomata , B= Dense inflammatory cells

Initial management consisted of topical steroid applications (triamcinolone with Orobace).

Due to the absence of any peri-anal disease or definitive systemic disease, systemic medication was not prescribed. After 2 months of local therapy the upper lip swelling had progressively worsened. Intralesional triamcinolone (40mg/mL) was then administered to the upper lip under general anaesthesia. (Figures 3a, 3b)

Figure 3a. Patient 1 with significant upper lip cheilitis granulomatosis prior to intralesional therapy

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Figure 3b. Patient 1 undergoing administration of intralesional triamcinolone under general anaesthesia



At 1 month post-intralesional steroids injections the upper lip swelling had significantly reduced. There was also improvement in both the gingival and mucosal health. Six-months following the steroid injections, all the oral signs and symptoms had remained stable. Patient has since been regularly reviewed by the Department of Paediatric Dentistry. During this time no further symptoms or relapses had developed. (Figures 4a, 4b)

Patient 1 went on to develop hip synovitis with a suspected diagnosis of juvenile arthritis. He was subsequently regularly reviewed by a Paediatric Gastroenterologist, Paediatric Orthopaedic Surgeon and a Paediatric Rheumatologist.

Figures 4a, 4b. Patient 1: 3 years post-treatment showing resolution of upper lip cheilitis granulomatosis and reduced gingival and mucosal erythema and granulomatosis

4a.



4b.***Patient 2***

An 8-years and 3-month-old boy of Caucasian descent was referred to the Paediatric Dentistry Department by his Paediatrician for investigation of generalised lip swelling and chronic gingivitis. His past medical history included previous 5-day admission for peri-anal infection secondary to a *staphylococcus* and *streptococcus* infections which were managed with IV Clindamycin. He had a history asthma which had resolved and his medical history was otherwise unremarkable. There was no family history of inflammatory bowel disease.

Patient 2 first developed lip swelling 3 months prior to the time of the initial assessment. Over a 3 month period there were fluctuations in severity with a failure to resolve and he also experienced weight loss and general lethargy. There was also a 12-month history of vague

and inconsistent abdominal signs and including constipation, bloating and one episode of peri-anal infection and bleeding.

Initial extra-oral examination revealed significant enlargement of the both the upper and lower lips with widespread fissuring, angular cheilitis and perioral erythema. (Figure 5a, 5b) The gingiva and anterior labial mucosa was erythematous with an atypical appearance and the buccal mucosa exhibited a distinct cobblestone appearance. No ulcerations were present at the time of examination, however there had been a 6-month history of oral ulcerations, during which time he had reported significant pain and difficulty with eating.

Figure 5a. , 5b. Patient 2 with asymmetrical enlargement of the both the upper and lower lips with fissuring, angular cheilitis, and perioral erythema.

5a.



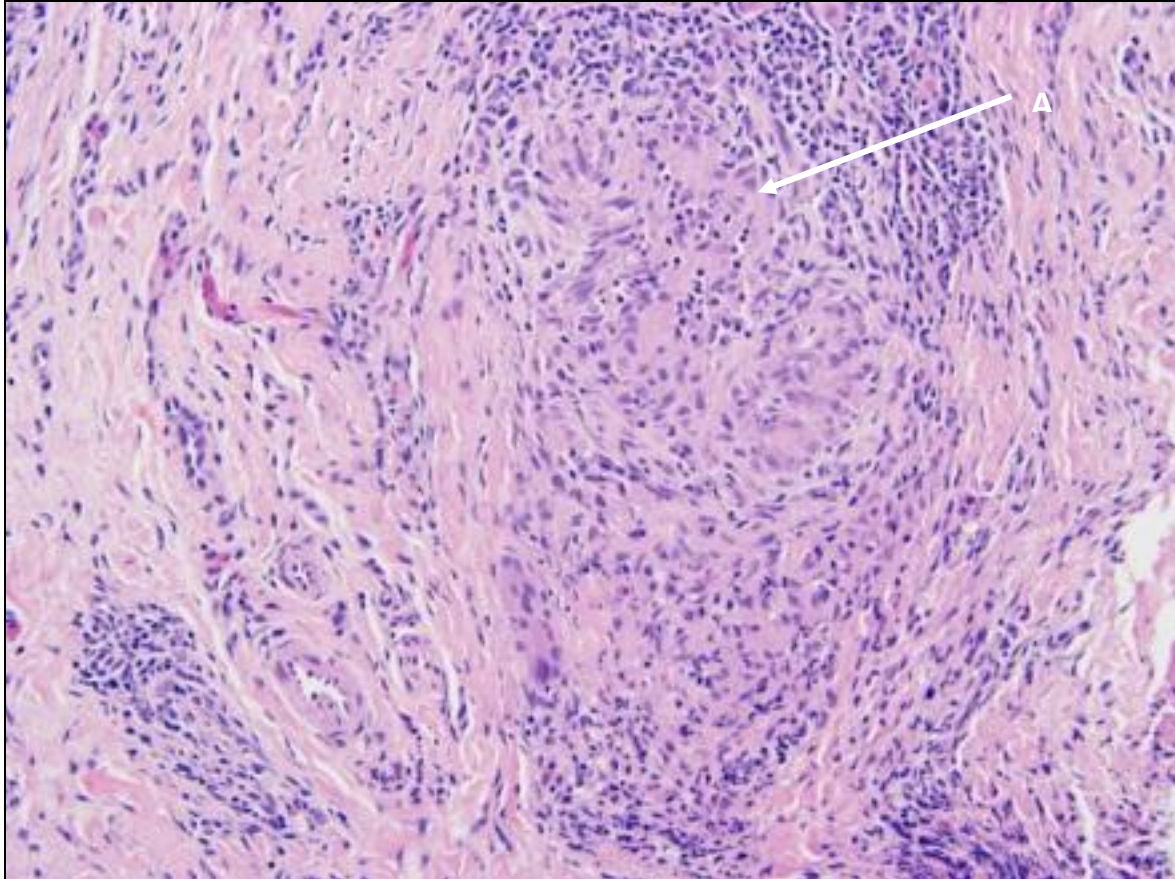
5b.

Multi-disciplinary investigations involving a Paediatric Dentist, Paediatrician and a Paediatric Gastroenterologist were conducted. Serological investigation indicated a positive ASCA and negative p-ANCA result, favouring a diagnosis of CD. All other testing was otherwise non-diagnostic for any other conditions. Furthermore, initial examination from the Paediatric Gastroenterologists revealed significant peri-anal disease. (Figure 6)

Figure 6. Patient 2 with a peri-anal tag

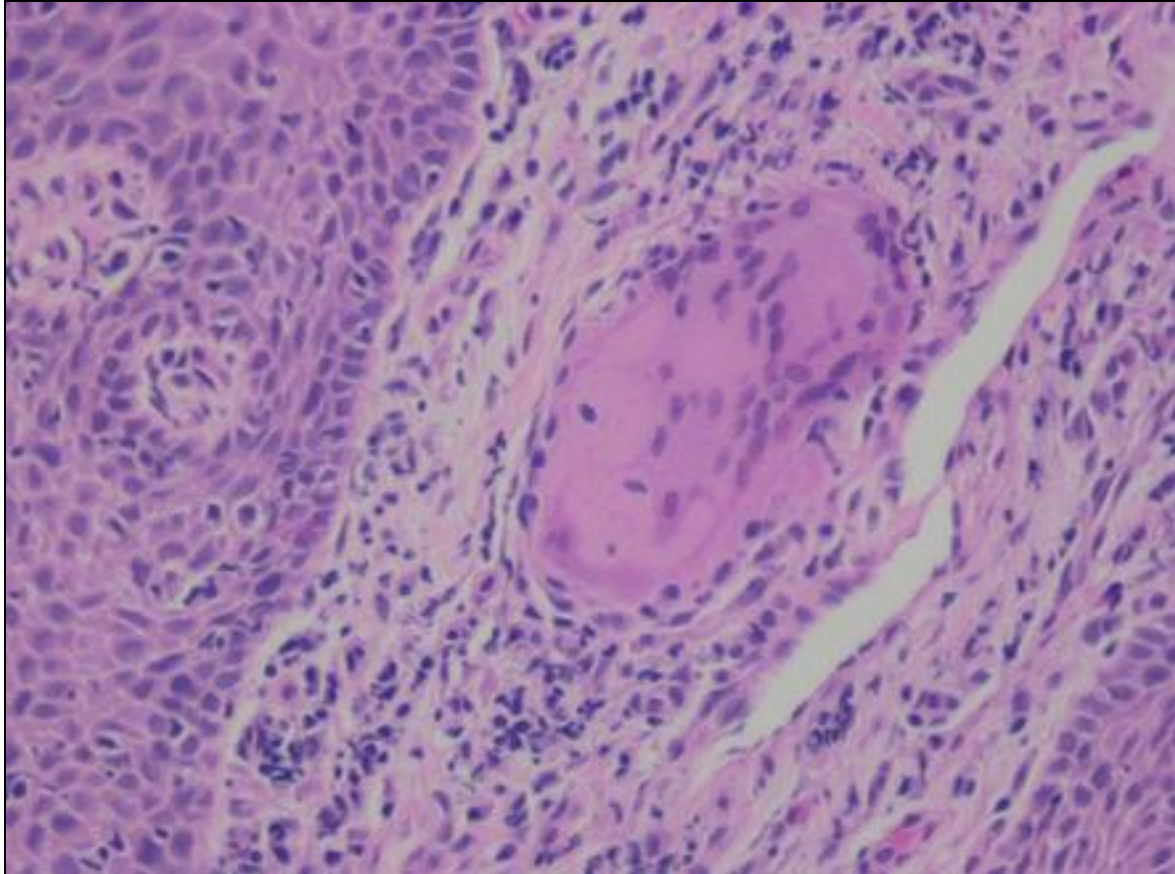
Under general anaesthesia, biopsies of the lower lip, right buccal mucosa and lower anterior gingival were taken by a Paediatric Dentist and a Gastroenterologist conducted an upper endoscopy and colonoscopy. Histological assessment of the buccal oral mucosa specimens showed stratified squamous epithelium deep to which was non-specific chronic granulomas, some containing multinucleate giant cells (Figures 6 a). The lip biopsy showed stratified squamous epithelium with sub-adjacent minor salivary glands present. Non-specific inflammation was seen in the sub epidermal tissues but no granulomas could be seen (Figure 6b). These findings are consistent with the clinical diagnosis of OFG. The colonoscopy showed fairly diffuse mild inflammation throughout the large intestine and in the terminal ileum. There were no granulomas noted and no superficial ulceration and the changes were microscopic rather than macroscopic. Significant peri-anal disease was also confirmed during the general anaesthesia.

Figure 6a: Buccal mucosal specimen at x10 magnification with non-specific granulomas and inflammation



A = Non-specific granuloma

Figure 6b. Lip biopsy specimen at x20 magnification with sub-epithelial non-specific inflammation and no granulomata present



As a result of the clinical, serological and histological findings a diagnosis of CD was made. Initial management consisted on Azathioprine 50mg daily and topical triamcinalone with Orabase for the lip swelling.

During the next 3-years the patient was followed up regularly by all relevant disciplines. His signs and symptoms associated with CD were controlled and managed with systemic medications, which included azathioprine, and prednisolone. Additionally metronidazole was prescribed during periods of significant peri-anal disease.

Three years following his initial diagnosis patient 2 redeveloped significant lip swelling and angular cheilitis. (Figure 7a, 7b) Initial management consisted of increased local therapies that were unsuccessful. A repeat upper endoscopy and colonoscopy was conducted to investigate any further intestinal involvement, and during the same procedure intralesional triamcinolone (40mg/mL) was injected into the upper and lower lips. Results of the endoscopies were normal and 1-month following the intralesional steroid injections the lip swelling had reduced considerably in size.

Figure 7a. Patient 2 at the time of presentation with upper lip enlargement and fissuring, angular cheilitis and perioral erythema.



Figure 7b. Patient 2 with significant erythematous anterior gingival and mucosal with an atypical appearance



Patient 2 remained on systemic medication for 5 years that was then ceased due to parental concerns. This resulted in almost immediate presentation of oral and peri-anal signs and symptoms that progressively worsened. Systemic therapy was recommenced approximately 2-months later that improved his peri-anal disease. The lip swelling did not respond to local or systemic therapies despite increases in his azathioprine dose. The lip swelling was managed with intralesional triamcinolone (40mg/mL) under general anaesthesia. Within 12 months the lip swelling reoccurred and was treated by intralesional triamcinolone (40mg/mL) injections under general anaesthesia. This has resulted in a marked reduction in swelling. An upper endoscopy and colonoscopy performed at the time revealed normal results.

Discussion

Debate exists regarding nomenclature and the link between CD and OFG based on the similarities in underlying immunological mechanisms (Satsangi and Jewell 1994; Gibson, Wray et al. 2000; Tilakaratne, Freysdottir et al. 2008). There are published reports of OFG being an initial presentation or a concurrent feature of CD (Bogenrieder, Rogler et al. 2003; Leao, Hodgson et al. 2004). Potential reasons for the lack of investigation into the incidence and prevalence of OFG in any population are that OFG may be under or misdiagnosed since the orofacial clinical manifestation may be misleading (Bogenrieder, Rogler et al. 2003). It is reported that early recognition of OFG is challenging due to a 48% occurrence of atypical onset of OFG, resulting in delayed or only suspected diagnosis (Mignogna, Fedele et al. 2003).

OFG has a widely variable presentation that can be multiform, acute, recurrent and chronic. It involves atypical sites of the orofacial region such as one or both lips, chin, cheeks, periorbital area, zygomatic tissues, lymph nodes, eyelids and forehead (Wiesenfeld, Ferguson et al. 1985; Al Johani, Moles et al. 2009). OFG may present with single or multiple minor manifestations unilaterally or bilaterally (Mignogna, Fedele et al. 2003). Other clinical features include angular cheilitis, fissuring of the lips (median cheilitis), mucosal swelling, mucosal tags, gingival enlargement (granulomatous gingiva) (Al Johani, Moles et al. 2009) and fissuring of the tongue (lingua fissures) (Leao, Hodgson et al. 2004; Khouri, Bohane et al. 2005; Grave, McCullough et al. 2009).

It is recognised that in children there is a higher expression of the initial manifestation of CD by oral lesions which may occur years ahead of intestinal symptoms (Khouri, Bohane et al. 2005),(Dupuy, Cosnes et al. 1999). Onset of oral lesions may precede (Plauth, Jenss et al.

1991) or establish at any time during the intestinal disease (Basu and Asquith 1980; Scully, Cochran et al. 1982; Harty, Fleming et al. 2005). Pittock *et al.* (2001) also found that children with OCD at the time of examination were more likely to have macroscopic and microscopic disease proximally in the gastrointestinal tract. Those with OCD had a shorter duration of systemic symptoms before presentation, but this did not reflect on the severity of oral symptoms (Pittock, Drumm et al. 2001). Other extra-intestinal symptoms of CD include the development of articular, ocular, dermatological, renal and liver manifestations (Tonkovic-Capin, Galbraith et al. 2006).

There are reports of OFG presenting and being diagnosed between 6 to 9 years of age, and comparatively earlier than the diagnosis of CD in children (Plauth, Jenss et al. 1991; Dupuy, Cosnes et al. 1999). It has been found that there is a greater incidence of OCD in males at a young age of onset (Walker-Smith 1994).

These findings apply to both cases outlined above. Both patients were male and were referred initially for investigation of orofacial symptoms in the absence of, or minimal abdominal symptoms. In both cases serology results favoured a diagnosis of CD and there was histological mild inflammation in the terminal ileum. Both patients were diagnosed with OFG based on clinical and histological features, however only patient 2 was further diagnosed with CD. This was based on the diagnosis of OFG, mild inflammation in the terminal ileum and significant peri-anal disease. Patient 1 also had some mild inflammation in the oesophagus but did not develop peri-anal disease. With positive serological markers for CD it suggests that patient 1 had yet to develop microscopic or macroscopic CD, thus the diagnosis of OFG may in fact precede a diagnosis of CD.

For both cases the OFG was initially managed by topical methods, but eventually treated by intralesional steroids. There are presently no published protocols for management of OFG. Sciubba *et al.* 2003 reported that adults patients managed with intralesional Triamcinolone injections responded well (Sciubba and Said-Al-Naief 2003). Therapy with injection of high concentrations of delayed-release triamcinolone acetonide (0.1%) was found to be most effective on moderate to severe and persistent facial and CG. Problems associated with this form of therapy were due to pain on application (Field and Tyldesley 1989) resulting in limitations to the volume of triamcinalone injected, especially in paediatric patients (Grave, McCullough *et al.* 2009). The provision of treatment under general anaesthesia was ideal as this alleviated any patient distress and discomfort experienced during the process. Although there are presently no published reports on the long-term outcome of intralesional corticosteroid therapy, the outcome in these patients has been successful in alleviating lip swelling.

With the severe and distressing presentation of orofacial signs and clinical symptoms at the time of consultation, topical therapy was initiated in preference to an elemental diet, as the latter would require a longer period of time to potentially obtain results. Cameron *et al.* (2003) recommended the use of an elemental diet in children and adolescents to avoid corticosteroid use and its potential effects on growth (Cameron and Middleton 2003), however its effectiveness in resolving OFG and sustaining remission of OFG has not been reported in other cases reports.

The comparative result between the two patients following treatment by intralesional steroids suggests that there may be further development of the oral disease process with increasing

age and this may be a causative factor in the relapses in lip swelling. Both cases also represent similar initial presentations with initial diagnoses of OFG, but differ in the diagnosis of CD. This may be a feature of CD and OFG and may be related to the age of the patient at the time of diagnosis.

These cases highlight the importance of a multidisciplinary approach to the management of these children. Combining investigative procedures and planned overall management of the oral, intestinal and peri-anal disease is crucial in achieving the best outcomes for the patients. Identification of a relationship between OFG and CD, such as OFG being a precursor to, or an early stage manifestation of CD in a paediatric population, could aid in diagnosis and enable early clinical management of the disease.

Chapter VI

Discussion

This study demonstrates that oral manifestations, including OFG are more common than indicated in the present data recorded on Australian paediatric CD patients. Although statistical significance could not be determined, from the reported GI and orofacial manifestations, clinical and serological investigations, and histopathological findings, the results from this study are inconclusive that OFG and oral manifestations are a precursor to onset of CD in a paediatric population.

Aim 1 of this study was to determine if oral manifestations, including OFG are a precursor to, or an oral manifestation of paediatric CD in an Australian population. In this study retrospective analysis of the APAIBDD found that 8.6% (81/945) of paediatric CD patients had oral manifestations, while in South Australia 9.3% (17/173) were recorded as having oral manifestations. This contrasts significantly to the 63.6% (14/22) diagnosed in this study. This discrepancy in diagnosis of oral manifestations is consistent with findings by Harty *et al.* (2005) in an Irish paediatric population where gastroenterologists failed to identify 55% (n=11) of oral lesions(Harty, Fleming et al. 2005).

Although the results from this study were insufficient to support that OFG is a precursor to paediatric CD, the two patients in the case report support that OFG is an oral manifestation of paediatric CD. Both patients presented with significant orofacial manifestations involving facial angioedema with marked facial and lip swelling and extensive cervical lymphadenopathy, and generalised lip swelling and chronic gingivitis. At the initial assessment patient 1 (aged 2 years and 3 months) had not reported GI symptoms and patient 2 (aged 8 years and 3 months) had experienced significant peri-anal disease, weight loss and lethargy. At the time of their respective oral biopsies, upper endoscopies and colonoscopies

were also taken. Their histological assessment was diagnostic for OFG whilst there was evidence of mild GI inflammation with the absence of granulomas. Serological investigation resulting in a positive ASCA and negative p-ANCA result favoured a diagnosis of CD despite the absence of GI histological pathology at the initial consultation and three years' post-diagnosis.

From this study the mean age of OFG diagnosis was 9 years and 6 months (SD 5.51 years, range, 2.24-14.35 years). Of the 14 patients with oral symptoms, 10 were boys and 4 were girls (5:2). The findings from this study is consistent with findings that there is a greater incidence of OCD in males at a young age of onset (Walker-Smith 1994) and with reports of OFG presenting and being diagnosed between 6 to 9 years of age, and comparatively earlier than the diagnosis of CD in children (Plauth, Jenss et al. 1991; Dupuy, Cosnes et al. 1999).

Aim 2 of this study was to establish if the oral manifestations are a separate oral pathological condition to CD based on clinical and histological similarities in South Australian paediatric patients. From the histological findings in this study, of the 6 (out of 8) patients with OFG only 1 patient had histological granulomatous lesions present in the GI tract. Thus this study was inconclusive for evidence to support a histological link between OFG and CD.

However, based on combine clinical, serological and histological findings 7 (out of 8) of the biopsied patients were diagnosed with OFG and CD, with 6 presenting with clinical perianal disease.

Aim 3 of this study was to use the data obtained to develop a visual diagnostic guide for OFG and orofacial manifestations. From the clinical investigations, the scores obtained from the OFG/Oral Manifestations Disease Activity Index and standardised extra and intra oral imaging (Appendix VI) were used to develop the visual diagnostic guide (see Appendix VII) required to evaluate the effectiveness of the visual diagnostic guide for OFG and orofacial manifestations of CD.

The hypothesis of this study was that the incidence and severity of OFG and other oral involvement have a role in paediatric CD. There were insufficient findings from this study to support this hypothesis. It has been reported that the onset of oral lesions may precede (Plauth, Jenss et al. 1991) or establish at any time during the intestinal disease (Basu and Asquith 1980; Scully, Cochran et al. 1982; Harty, Fleming et al. 2005). When assessing the OFG/Oral Manifestations Disease Activity Index (Appendix V) scores according to the number of extra and intra oral symptoms diagnosed and total scores obtained, it is proposed that the severity can be classified as none, mild, moderate and severe according to the following ranges:

Category	Score range
None	0-10
Mild	11-20
Moderate	21-30
Severe	31 <

Although the total maximum score possible was 160, from the 22 patients the highest score obtained was 55 for 2 patients and the overall mean score was 15 (SD 17.7).

These scores were then compared with CD activity determined by serological investigation. Active CD was diagnosed in 8 out of 21 patients (38%; 6 males, 2 females) and within this group, 5 patients had positive OFG/oral manifestation activity scores. The severe score of 55 was found for 2 males, mild for 2 male patients and 3 patients (1 male, 2 females) were classified as none. Borderline active CD was found in 2 patients (2 males) who were both classified as not having the OFG/Oral Manifestations Disease Activity Index scores. Of the 8 patients with non-active CD (4 males, 4 females) 1 female had a severe score of 50, 1 male with a moderate score of 25, 3 with a mild score (2 males, 1 female) and 3 with no oral activity scores. Further investigation is required to determine the accuracy and effectiveness of the OFG/Oral Manifestations Disease Activity Index to diagnosis the severity of orofacial manifestations. Although the link between the severity of OFG and other oral involvement with CD activity was inconclusive, 7 of the 22 patients reported that their oral and GI symptoms coincided, and 3 were unsure if there was a link.

The following methodological shortcomings were encountered in this study:

- Skewed sample of patients drawn from the APAIBCC with only South Australian CD patients selected and 1 patient with OFG only
- Lack of randomisation of patients
- Only a single clinical and serological investigation was conducted. Ideally a long term follow up would be conducted to investigate the oral manifestations and CD disease activity experienced
- Small sample size involved with the clinical study

With the small sample size and skewed sample of patients, this study was unable to obtain statistically significant results. The greatest difficulty encountered during this study was to

obtain a sufficient sample size. From the South Australian paediatric CD data base, all 58 eligible patients were invited to participate. Participants and their families were contacted via two mail-outs consisting of a letter of invitation (Appendix VII), information sheet (Appendix VIII) and the consent form (Appendix IX), and a follow-up phone call. Only 25 participants consented to participate and from this sample 2 later withdrew as the patients no longer wished to participate, and 1 was insufficiently co-operative for the clinical assessment. Additionally 1 patient failed to attend for serological investigations following their clinical assessment.

This study included the following strengths:

- Clinical assessment was conducted by the primary investigator and two paediatric dental consultants resulting in minimising variance between the clinicians

The implications of this study are that:

- The reported incidence of OFG and oral manifestations in Australian paediatric patients with CD by non-dental clinicians is lower than that found by dental clinicians, indicating that there is the potential for oral symptoms to be under reported on the APAIBDD
- Use of the visual guide and scoring system by non-dental clinicians could aid diagnosis and assessment of the severity of oral manifestations
- From the results obtained, the importance of a multi-disciplinary approach to investigate oral and GI disease is highlighted. This supports that standardised investigation protocols could be established for patients presenting with OFG and other orofacial manifestations should involve both dental practitioners and non-dental

clinicians i.e. gastroenterologists. Successful management of oral and GI symptoms and disease activity can also be obtained through a multi-disciplinary approach

Future research directions following this pilot study include:

- Involvement of other Australian tertiary hospital institutions with paediatric dental and gastroenterology units there can be further investigation into the incidence and severity of oral manifestations in an Australian paediatric population with CD
- Correlate the oral clinical presentation and severity index scores with PCDAI clinical index scores to assess if there is concurrent disease activity and severity
- Further investigation into management protocols for OFG and other oral manifestations of paediatric oral CD i.e. use of dietary modifications and other topical therapies compared to steroidal injections and systemic therapies
- Further investigation into the effectiveness of the visual guide by non-dental clinicians for diagnosis of OFG and other oral manifestations
- Further investigation into the accuracy and effectiveness of the OFG/Oral Manifestations Disease Activity Index

Chapter VII

Conclusion

Findings from this study support the notion that oral manifestations may be under diagnosed with a discrepancy found between diagnosis by non-dental and dental clinicians. While OFG may occur with or without any microscopic changes in the gastrointestinal tract, it has a widely variable presentation and early diagnosis may be challenging due to the atypical onset. Use of a universal oral disease activity index and visual guide may aid future diagnosis and assessment of the condition.

This study is the first to publish data relevant for a South Australian paediatric population with Crohn's disease. The methods used for the combined clinical and serological assessment can be applied to larger studies involving other tertiary paediatric hospitals involved with the Australian Paediatric and Adolescent Inflammatory Bowel Disease Database. Through involvement of patients managed through a single institution, there was consistent ease of access to the various data required. Additional benefits from this study were that a majority of the paediatric patients with Crohn's disease had their first comprehensive oral assessment for oral manifestations of Crohn's disease.

It was identified that multiple patients had initially experienced oral symptoms prior to any manifestations of gastrointestinal symptoms. There was acknowledgement by the participants and/or their parents that if more was known about the potential link between orofacial symptoms and Crohn's disease, potentially earlier assessment and diagnosis of the oral manifestations could lead to earlier investigations of Crohn's disease. This could then have aided in lessening the morbidities and comorbidities experienced.

With the known strong association between OFG and CD, multidisciplinary management is recommended to establish a definitive diagnosis.

Appendices

I. Women's and Children's Human Ethics Approval Letter



Government of South Australia
SA Health



Women's
& Children's
Hospital

4th March 2009

Dr E Yeung
Paediatric Dental Dept
CYWHS

Research Secretariat
72 King William Road
North Adelaide SA 5006
Tel 08 8161 6521
Tel 08 8161 6390
Fax 08 8161 8177
www.cywhs.sa.gov.au

Dear Evelyn

Re: Incidence and prevalence of Orofacial Granulomatosis and other oral involvement in a paediatric population with or without Crohn's Disease. REC2111/10/11

I refer to your letter dated 16th February 2009 in which you responded to matters raised by the CYWHS Human Research Ethics Committee at its October 2008 meeting. I am pleased to advise that your protocol has been granted full ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

You are advised that if now, or in the future, the study involves non CYWHS staff or students, a signed Confidentiality Agreement will be required and, if they visit any CYWHS site, a National Police Certificate provided to the Ethics Committee and the Human Resources Department. The study may proceed on this proviso.

I remind you approval is given subject to:

- immediate notification of any serious or unexpected adverse events to subjects;
- immediate notification of any unforeseen events that might affect continued ethical acceptability of the project;
- submission of any proposed changes to the original protocol. Changes must be approved by the Committee before they are implemented;
- immediate advice, giving reasons, if the protocol is discontinued before its completion;
- submission of an annual report on the progress of the study, and a final report when it is completed. Please note it is your responsibility to provide these reports – without reminder from the Ethics Committee.

Approval is given for three years only, and if the study is more prolonged than this, a new submission will be required. Please note the approval number above indicates the month and year in which approval expires and it should be used in any future communication.

If University of Adelaide personnel are involved in this project, you, as chief investigator must submit a Human Research Approval notification form online at <http://www.adelaide.edu.au/ethics/human/guidelines/> within 14 days of receiving this ethical clearance to ensure compliance with University requirements and appropriate indemnification.

Yours sincerely

TAMARA ZUTLEVIC (DR)
CHAIR
CYWHS HUMAN RESEARCH ETHICS COMMITTEE

Protocol For Dental Clinical Assessment

1. Sign consent forms in front of parent (*5 minutes*)
 - a. Research participation
 - b. Clinical photography

2. Go through Research Questionnaire (Parents/patient form)- (*15 minutes*)

3. Clinical assessment
 - a. General visual dental examination (see form)
 - b. OFG/Oral manifestations Activity Index (see form)

(Examiner 1- *10 minutes*)

(Examiner 2- *10 minutes*)

4. Photographic records- patients to attend WCH Photography Unit
Centre for Education and Training- located within the Centre on level 1, Samuel
Way Building

Sites to photograph: (as per Guide- see Appendix VI)

5. Patient to attend Pathology for required blood tests
 1. Full blood count- iron levels, Vitamin B12, ESR, C-reactive protein
 2. ASCA (anti-Saccharomyces cerevisiae antibodies)
 3. ANCA (anti-neutrophil cytoplasmic antibodies)
 4. p-ANCA (ANCA with perinuclear staining)

II. Questionnaire

Patient Name:.....Date:.....

PAST MEDICAL HISTORY			
Pregnancy			
Birth			
- Gestation Period			
- Method of delivery			
- Weight			
- Complications			
History of Serious Illnesses			
Name of Specialists involved with treatment			
Name of General Practitioner			
Any other specific medical condition			
MEDICAL HISTORY		NAME	REACTION
Allergies			
	Medication		

	Foods		
Immunization			
Medications			
CVS			
CNS			
Respiratory			
Renal/Hepatic			
History of Rheumatic Fever			
Endocrine			
Haematology			
Oncology			
Urinary Tract			

Other	
Gastrointestinal <ul style="list-style-type: none"> - Specialist - Diagnosis - Date of Diagnosis 	
Family History	
Social History	

PAST DENTAL HISTORY	
- Previous experiences	
- Types of treatment	
- Where the treatment has occurred	
- Outcomes of treatment	

SPECIFIC QUESTIONS FOR CROHN'S DISEASE

1. What gastro-intestinal symptoms did your child have prior to the diagnosis of OFG/CD?

SYMPTOM	YES	NO	Details
Weight loss			
Malaise			
Constipation			
Diarrhoea			
Abdominal Pain			
Bloating			
Blood in the stool			
Absence from school			
Lethargy			
Other			

2. At what age did your child first have gastro-intestinal symptoms?

.....YEARS.....MONTHS

3. If yes, at what age was this child diagnosed with gastro-intestinal symptoms?

.....YEARS.....MONTHS

4. Did your child have any oral signs or symptoms- (please tick)

SYMPTOM		YES	NO	DETAILS
Swelling of the lips	Upper			
	Lower			
	Both			
Fissure/cracks in affected lips				
Redness around the mouth				
Dry/flaky skin around the mouth/lips				
Corners of the mouth red/dry/cracked				
Facial asymmetry				
Facial palsy				

Eye involvement			
Gum tags			
Swelling of the gums			
Swelling of the cheeks			
Lumps/cobble stoning of the cheeks			
Other			

5. If yes, did these oral signs & symptoms come and go? Or were they persistent?

6. If yes- did these signs and symptoms proceed or follow any gastro-intestinal signs/symptoms?

7. If yes- were these oral signs/symptoms investigated?

YES/NO.....

8. If yes- what type of investigation(s) were undertaken?

Oral biopsy/ Other

YES/NO.....

9. Did the oral signs/symptoms relate to the intensity of symptoms of Crohn's disease

YES/NO.....

10. Were there any triggers such as specific foods which intensified the oral signs and symptoms?

YES/NO.....

11. Have the oral signs/symptoms resulted in any psychological issues

YES/NO.....

12. Are they currently under the management of a dentist/Oral Maxillo Facial Surgeon/Paediatric Dentist?

YES/NO

13. If oral signs and symptoms were present, were there any peri-anal changes?

YES/NO.....

14. If the child had only oral signs and symptoms, did they have an endoscopy and/or colonoscopy following this?

YES/NO Endoscopy/colonoscopy

Was a diagnosis of Crohn's Disease or other established?

YES/NO.....

15. If the diagnosis of Crohn's Disease was established, did the systemic medication result in improvement in oral signs and symptoms?

YES/NO.....

16. What systemic medication were they given?

.....

17. Were any local measures such as topical or intra-lesional steroids used to reduce oral signs and symptoms?

.....

18. Do you think the involvement of Paediatric dentist is indicated for children diagnosed with Crohn's Disease?

YES/NO.....

19. Any other comments or questions?

.....
.....
.....
.....
.....

***III. Oral health assessment form from the Oral Health Surveys
(World Health Organisation (Geneva, 1997))***

NOTE:

This appendix is included on pages 179-182 of the print copy of the thesis held in the University of Adelaide Library.

IV. OFG/Oral Manifestations Disease Activity Index

1. Patients Full Name:

.....

Date:/...../.....

Age:years..... months

Gender: Male/Female

Each parameter must be assigned a value

Height:.....

Weight:.....

Extra Oral

		Score	Subtotal
Lip swelling	None	0	
	Asymmetrical	5	
	Symmetrical	5	
	Maxillary lip	5	
	Mandibular lip	5	
Angular cheilitis	None	0	
	Unilateral	5	
	Bilateral	10	
Lip fissuring/cracks	None	0	
	Single	5	
	Multiple	10	
Skin- red/flaky	None	0	
	Localised	5	
	Generalised	10	
Facial asymmetry	None	0	

	Unilateral	5	
	Bilateral	10	
Cheek swelling	None	0	
	Unilateral	5	
	Bilateral	10	
Chin swelling	None	0	
	Unilateral	5	
	Bilateral	10	
Eye involvement	None	0	
	Unilateral	5	
	Bilateral	10	
Facial palsy	None	0	
	Unilateral	5	
	Bilateral	10	

Intra Oral

		Score	Subtotal
Tongue-fissures	None	0	
	Single	5	
	Multiple	10	
Gingival swelling	None	0	
	Localised	5	
	Generalised	10	
Gingival tags	None	0	
	Single	5	
	Multiple	10	
Mucosal tags	None	0	
	Localised	5	
	Multiple	10	
Ulcers	None	0	
	Single	5	
	Multiple	10	
Cobblestone mucosa	None	0	
	Unilateral	5	
	Bilateral	10	
		TOTAL SCORE	

V. Guide: Standardised views for clinical extra and intra oral imaging





VI. Orofacial Granulomatosis/Oral Crohn's Disease Diagnostic Guide

OROFACIAL GRANULOMATOSIS/ORAL CROHN'S DISEASE
DIAGNOSTIC GUIDE

EXTRA ORAL

NORMAL

ACTIVE DISEASE

ANGULAR CHELITIS



FACIAL ASYMMETRY AND CHEEK SWELLING



LIP FISSURES AND CRACKS



OROFACIAL GRANULOMATOSIS/ORAL CROHN'S DISEASE
DIAGNOSTIC GUIDE

EXTRA ORAL

NORMAL

ACTIVE DISEASE

LIP SWELLING

Upper Lip



Lower Lip



Upper and Lower Lips



OROFACIAL GRANULOMATOSIS/ORAL CROHN'S DISEASE
DIAGNOSTIC GUIDE

EXTRA ORAL

NORMAL

ACTIVE DISEASE

SKIN INVOLVEMENT



OROFACIAL GRANULOMATOSIS/ORAL CROHN'S DISEASE
DIAGNOSTIC GUIDE

INTRA ORAL

NORMAL

ACTIVE DISEASE

GINGIVAL SWELLING



GINGIVAL TAGS



MUCOSAL TAGS



VII. Letter of invitation for participation

30th of March 2009



Government of South Australia
Children, Youth and Women's
Health Service



**Women's
& Children's
Hospital**

To the Parent of

72 King William Road
North Adelaide SA 5006
Tel 08 8161 7000
Fax 08 8161 7459
www.cywhs.sa.gov.au

The Gastroenterology Unit and the Dental Department have noticed several children who have been diagnosed with Crohn's Disease also presented with oral changes, such as lip swelling, mouth ulcers. As a result, further research will be conducted into the relationship between the oral changes and Crohn's Disease.

The general aim of this study is to identify the relationship between oral changes and Crohn's Disease which may result in earlier diagnosis and a greater understanding of Crohn's Disease in children. This study will audit information regarding oral and intestinal signs and symptoms, and is not a clinical investigation that is part of your child's ongoing management of Crohn's Disease.

You and your child are invited to participate in this study; participation in this study is entirely voluntary. Your child's participation in this study will be valued in ongoing research in Crohn's Disease in children.

This information sheet has been mailed out by the Gastroenterology Unit, and no patient information has been provided to the primary researcher Dr Evelyn Yeung.

If you have any questions please do not hesitate to contact Dr Evelyn Yeung, Dental Department Women's and Children's Hospital. (08) 8161 7379

Please find attached an information sheet and consent form for the study.

Thank you for considering our request.

Dr Sam Gue,
MDS, FRACDS, FRACDS (Paed), FICD
Head of Department Paed. Dentistry
Women's and Children's Hospital

Dr David Moore,
MBBS, FRACP
**Medical Unit Head of the
Gastroenterology Department**
Women's & Children's Hospital

Dr Evelyn Yeung
BDS,
Paediatric Dental Registrar
Women's and Children's Hospital

VIII. Information sheet for participants

NOTE:

This appendix is included on pages 193-194 of the print copy of the thesis held in the University of Adelaide Library.

IX. Consent form for participation

**CHILDREN, YOUTH & WOMEN'S HEALTH SERVICE
(CYWHS)
HUMAN RESEARCH ETHICS COMMITTEE (HREC)**

CONSENT FORM

TITLE

Oral Changes in a Paediatric Population with or without Crohn's Disease

I _____

hereby consent to my child's involvement in the research project entitled:

1. The nature and purpose of the research project described on the attached Information Sheet has been mailed to me. I understand it and agree to (my child) taking part.
2. The privacy and confidentiality of any information I provide will be safeguarded as explained in the Participant Information Sheet.
3. I understand that my child's medical records will be accessed throughout the study.
4. I understand that I and/or my child may not directly benefit by taking part in this study.
5. I acknowledge that there is possible discomforts and inconveniences, as outlined in the Information Sheet that was sent to me.
6. I understand that I can withdraw my child from the study at any stage and that this will not affect medical care or any other aspects of my/my child's relationship with this healthcare service.
7. I understand that there will be no payment to me/my child for taking part in this study, although there will be reimbursement of travel expenses.
8. I have had the opportunity to discuss taking part in this research project with a family member or friend. I have had the option/opportunity to discuss this research project with the researcher in the presence of a family member or friend present if I desired.
9. I am aware that I should retain a copy of the Consent Form, when completed, and the Information Sheet.
10.
 - a) I do/do not consent to a specimen of blood being taken from my child and being used in this research project.

- b) I do/do not consent to a clinical examination being used in this research project.
- c) I do/do not consent to clinical photographs of my child being used in this research project.

- 11. I understand that any information obtained from this research will only be used in future research if consent is re-obtained, and as approved by the Children's, Youth and Women's Health Service Human Research Ethics Committee.
- 12. I understand that I am free to stop participating at any stage, and withdraw the use of clinical photographs, without giving any reason, and that my action of donating/not donating a sample will not affect any other aspect of my/my child's relationship with this healthcare service.any other aspects of my/my child's relationship with this healthcare service.
- 13. I understand that my/my child's information will be kept confidential except in the case of a legal requirement to pass on personal information to authorised third parties. The requirement is standard and applies to information collected both in research and non-research situations. Such requests to access information are rare however we have the obligation to inform you of this possibility.

Signed:

Relationship to Patient:

Full name of patient:

Dated:.....

I certify that I have explained the study to the parent and child and consider that he/she understands what is involved.

Signed:

Dr Evelyn Yeung, Primary Researcher, Paediatric Dental Registrar,
Department of Paediatric Dentistry

Dated:

X. Summary of oral histopathological features in each patient

Patient	Histological Features
A	Cheek Parakeratotic squamous epithelium Heavy chronic inflammatory infiltrate in sub epithelial tissues Scattered small granulomata with occasional giant cells Small central area of ulceration
B	Lower Lip Stratified squamous non-keratinising epithelium Sub epithelial connective tissue including minor salivary gland lobules Mild non-specific inflammatory changes with scattered lymphocyte and plasma cells within the sub epithelial connective tissue and salivary lobules No granulomatous inflammation is seen
C	Cheek (left) Non-keratinising acanthotic stratified epithelium Patchy parakeratosis Mild to moderate inflammatory infiltrate in sub epithelial connective tissues with scattered lymphocytes, plasma cells and occasional eosinophils Granuloma with multinucleated giant within skeletal muscle Superficial microscopic granuloma
D	Cheek (right) Non-keratinising stratified squamous epithelium with acanthosis and pseudoepitheliomatous hyperplasia Moderate epidermal spongiosis with moderate lymphocytic exocytosis. Superficial sub epithelial stroma with mononuclear inflammatory infiltrate & plasma cells Noncaseating granulomata within deep subepithelial connective tissue and interposed between skeletal muscle bundles Granulomata composed of multinucleated giant cells and epithelioid macrophages, associated with small numbers of lymphocytes
	Lower Lip Multiple noncaseating granulomata associated with minor salivary glands and within the stromal collagen. Granulomata are composed of multinucleated giant cells, epithelioid macrophages and associated lymphocytes
E	Lower lip, right cheek, labial mucosa anterior mandible Non keratinizing squamous epithelium with underlying dermis Widespread dermal infiltration including epithelioid histiocytes, multinucleated giant cells Granulomata mixed with lymphocytes, plasma cells and eosinophils. Inflammatory infiltrate blood vessels within the dermis No evidence of necrosis
F	Left attached gingiva Chronic inflammatory infiltrate is seen in periductal and periglandular areas consisting of lymphocytes and plasma cells Chronic inflammation in the interface of epithelium and underlying dermis No granulomas are seen
G	Right attached gingiva Stratified squamous mucosal epithelium with parakeratosis, acanthosis, spongiosis and several micro-abscesses in the superficial layers

Lymphocyte and neutrophil exocytosis is present
Pseudoepitheliomatous hyperplasia
Intense chronic inflammatory infiltrate in connective tissue
Lymphohistiocytic in nature with numerous plasma cells and occasional eosinophils and neutrophils
Perivascular and interstitial inflammation extending to the epithelial-stromal interface
Several noncaseating granulomata within the connective tissue
Connective tissue appears oedematous and myxoid

H

Lower Lip

Non-specific inflammation in the sub epidermal tissue but no granulomas can be seen

Mandibular anterior labial mucosa

Stratified squamous epithelium with non-specific chronic inflammation including granulomas, some containing multi-nucleate giant cells

XI. Summary of significant GI lesions histological features identified in each patient

Patient	Histological features
A	Duodenum Mild increase in intra-epithelial lymphocytes at the tips of some villi
B	Oesophagus Increased lymphocytes within epithelium with mild basal hyperplasia and focal prolongation of the connective tissue papillae Gastric antrum Increase in plasma cells within the lamina propria
C	Oesophagus Moderate inflammation with numerous lymphocytes within the surface epithelium and scattered lymphoid and plasma cells in the sub-epithelial connective tissues Gastric body and antrum Numerous lymphocytes within the epithelium associated with marked basal layer hyperplasia and prolongation of the connective tissue papillae. Scattered histiocytes within the connective tissue papillae Ileum Several poorly formed granulomas Caecum Increased numbers of plasma cells and eosinophils within the lamina propria with a poorly formed mucosal granuloma Colon Marked expansion of inflammatory cells in the lamina propria and mild goblet cell depletion Splenic flexure Mild chronic colitis present Sigmoid colon Moderate chronic inflammation with a possible granuloma within the mucosal lymphoid aggregate Rectosigmoid Chronic inflammation with patchy goblet cell depletion with 2 mucosal granulomas Rectum Mucosal granuloma incorporating a giant cell and mild chronic inflammation
D	Oesophagus Increased intraepithelial lymphocytes Gastric antrum Lymphoid aggregates inclusive of epithelioid macrophages in keeping with granulomata Duodenum Increased numbers of mononuclear inflammatory cells within the lamina propria
E	Oesophagus Mild oesophagitis present with occasional intraepithelial eosinophils Terminal ileum Mildly hypercellular lamina propria with isolated neutrophils within the crypt epithelium
F	Duodenum Increased inflammatory infiltrate with polymorphs in the lamina propria Hepatic flexure and transverse colon Ulcer and an increase in inflammatory cells in the lamina propria with polymorphs also seen Splenic flexure Increase in the inflammatory cells in the lamina propria. Crypt abscess is seen and

- ulcer debris
- Rectosigmoid
 - Base of an ulcer consisting of granulation tissue comprising of lymphocytes and polymorphs
- Rectum
 - Irregular gland structure and an increase in inflammatory infiltrate with infiltration of polymorphs
- G** Sigmoid
 - Mild increase in inflammation in the lamina propria including crypt abscesses and goblet cell preservation
- H** Sigmoid
 - Goblet cell preservation with a slight increase in eosinophils and lymphocytes in the lamina propria



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