

Disorders of the Orofacial and Gastrointestinal Tract

A study with special reference to Orofacial Granulomatosis and Crohn's disease

Akademisk avhandling

som för avläggande av odontologie doktorsexamen vid
Göteborgs Universitet kommer att offentligens försvaras i
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av
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Avhandlingen baseras på följande delarbeten:

- I. G Gale, S Östman, E Rekabdar, Å Torinsson Naluai, K Högkil, B Hasséus, R Saalman, M Jontell
Characterisation of a Swedish cohort with orofacial granulomatosis with or without Crohn's disease. *Oral Diseases* (2014) doi:10.1111/odi.12236
- II. G Gale, S Östman, R Saalman, E Telemo, M Jontell, B Hasséus
Immunophenotype in orofacial granulomatosis with and without Crohn's disease. *Med Oral Patol Oral Cir Bucal* (2014) 19;6
- III. G Gale, G V Sigurdsson, S Östman, P Malmberg K Högkil, B Hasséus, M Jontell and R Saalman
Does Crohn's disease with concomitant orofacial granulomatosis represent a distinctive disease subtype?
In manuscript
- IV. G Gale, AP Molina Vivas, G Porta, F D'Almeida Costa, G Warfvinge, F de Abreu Alves, M Jontell, R Saalman
Nodular tongue syndrome – characterisation of the immunohistology of a novel clinical disorder in organ transplanted children
In manuscript



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Abstract

Orofacial granulomatosis (OFG) is a rare granulomatous disease primarily affecting children and adolescences causing lesions in the oral and facial regions such as lip/facial swelling, angular cheilitis, tag formation, mucosal ridges, cobblestone phenomenon and full thickness gingivitis. Crohn's disease (CD), on the other hand, is a chronic inflammatory bowel disease presenting with intestinal inflammation that may involve any area of the gastrointestinal tract. The association between OFG and CD has been known for several decades as the two conditions share both clinical and histopathological features, but the exact connection is as yet unclear. Nodular tongue syndrome (NTS) is a unique clinical appearance seen in some paediatric liver recipients. In addition, they also develop OFG like features such as lip swelling, angular cheilitis, cobblestone phenomenon and hyperplastic gingiva.

The overall scientific questions that were asked prior to the commencement of this thesis were (i) do CD and OFG represent distinctive disorders when they appear separately or in combination and (ii) do oral lesions seen in paediatric liver recipients stem from the same disease spectrum as orofacial granulomatosis? In the first and second study the clinical and histopathological features of patients with OFG solely (OFG-S) were compared with patients suffering from OFG and concomitant CD. The first study also included a genetic comparison of nucleotide-binding oligomerization domain-containing protein 2 (NOD2) variations. The NOD2 protein acts as a bacterial sensor recognising muramyl dipeptide, which is a specific structure in the wall of Gram-positive and Gram-negative bacteria. In the third study, patients with CD+OFG were compared with a reference group of patients with only CD (CD-R) regarding clinical features. In the fourth study, children who had been subjected to solid organ transplantation and afterwards developed clinical features similar to OFG were investigated regarding the immune response.

No significant differences in the clinical presentation of oral lesions between OFG-S and OFG+CD were found. However, the OFG-S patients perceived their overall discomfort, aesthetic problems and social discomfort as more severe than the OFG+CD patients. None of the patients with OFG carried any of the NOD2 variations whereas four out of the 12 patients with OFG+CD had a NOD2 variant (Arg702Trp). Immunohistochemical analyses revealed a significantly higher number of CD3-expressing T cells and CD11c-expressing dendritic cells in the connective tissue of patients with OFG-S compared to patients with OFG+CD. Mast cells displayed a high level of activation, although no significant difference was detected when comparing the two groups. The proportion of patients with intestinal inflammation in the upper gastrointestinal tract was significantly greater in the CD+OFG group compared to the CD-R group. Ileocolonic inflammation as well as granuloma formation was also significantly more common in the CD+OFG patients than in the CD-R group. In addition, perianal disease was more common in the patients with CD+OFG. NTS, which some paediatric liver recipients develop, is a longstanding clinical disorder representing swollen fungiform. The immunohistochemistry revealed an infiltrate composed positive T-cells, B-cells, macrophages and plasma cells, but no granulomas were found. One of the important clinical observations made in this thesis was that orofacial granulomatosis in conjunction with Crohn's disease (CD+OFG) signals a more advanced disorder that may demand a more intensive treatment approach.

Key words: Orofacial granulomatosis, Crohn's disease, nodular tongue syndrome

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