Graves' ophthalmopathy: in search of better markers and better treatment

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Graves' ophthalmopathy is an autoimmune disorder closely related to Graves' hyperthyroidism. Autoimmune mediated inflammatory responses in the orbital tissues takes place which leads to swelling of extra ocular muscles and an increase in orbital fat. These features give rise to symptoms such as eyelid swelling and retraction, proptosis, eye muscle motility disturbances and in severe cases optic neuropathy. Apart from improving visual functions one also has to consider restoration of appearance when treating GO patients.

In the first part of this thesis we search for a serum marker, which could be used to select GO patients who might benefit from immunosuppressive treatment. The studies described in Chapter 2, 3 and 4 are all performed in GO patients compared with healthy controls, matched for sex, age and smoking habits. In Chapter 2 it is demonstrated that serum concentrations of several cytokines are increased in GO patients compared with controls. A combination of IL-6, sCD30 and TNFαRI has some value for predicting response to radiotherapy, but is less useful for daily clinical practice. Serum IL-18 measurements have no value in the management of GO patients, because the concentrations are similar in GO patients and matched controls (Chapter 3). sICAM-1, sVCAM-1 and sELAM-1 serum values (all adhesion molecules) are all increased in serum of GO patients compared with controls (Chapter 4). Serum levels in patients with Graves' disease without ophthalmopathy were comparable to those of controls, so the higher figures in GO patients are probably due to the eye disease itself and not to the thyroid disease. In patients and in controls the serum levels of adhesion molecules were correlated with smoking, with sICAM-1 levels being higher in smokers than non-smokers and sVCAM-1 levels being lower in smokers than non-smokers. In addition, some serum cytokines (i.e. IL-1RA and IL-6R) were increased in smokers compared with non-smokers. A correlation between sICAM-1 levels and the severity of GO but not with the activity of GO is disclosed. There is however, a wide overlap in serum cytokine and adhesion molecule concentrations between healthy controls and GO patients, as well as between responders and non-responders to radiotherapy within the group of GO patients. Taken together, we have not found a clinically applicable biological serum marker for GO.

Because molecules measured in serum are at most a weak reflection of the situation in the inflamed orbital tissues, we studied the cytokine network in orbital fat/connective tissue samples of GO patients, which is described in Chapter 5. We found with quantitative PCR that in orbital fat/connective tissue samples of GO patients with active untreated eye disease the mRNA expression of several proinflammatory and Th1 cytokines are increased compared with the mRNA expression in orbital tissues of inactive GO patients. The mRNA expression of Th2 cytokines is comparable. These findings imply that GO starts primarily as a Th1 disease. Based on our results, research towards innovative treatment of GO patients might be suggested with selective immunosuppressive drugs counteracting Th1 and/or proinflammatory cytokines. Especially IL-1RA seems to hold much promise, but additional research is warranted. We also found that TSH-R mRNA is more often present in orbital fat/connective tissue of active GO patients compared with GO patients with inactive eye disease. This could mean that orbital fibroblasts express the TSH-R only during certain stages of differentiation or under certain conditions. The precise role of the TSH-R is to be determined.

The second part of this thesis deals with aspects of medical and surgical management of GO. In Chapter 6 we prospectively studied 15 patients with very active GO and signs of optic neu-
ropathy, which can become legally blind if not treated prompt and adequately. We hypothesized that surgery by itself might inactivate the eye disease, and that immunosuppressive therapy, with possible severe side effects would not be necessary in the active inflammatory stage. Patients were randomized to receive either methylprednisolone pulse therapy or decompressive surgery. In this small group of patients we found no significant difference in outcome although most patients primarily assigned to surgery, later still needed immunosuppressive therapy. In the steroids group, half of the patients needed decompressive surgery. At the end of our follow-up, most patients had obtained a near normal visual acuity. It is recommended to treat patients with optic neuropathy with methylprednisolone pulse therapy first, and when there is insufficient improvement of the visual acuity to perform acute decompressive surgery. Chapter 7 deals with the long-term side effects of orbital irradiation. We performed a follow-up study (mean follow-up 10 years) in a cohort of 245 GO patients to evaluate the frequency of long-term complications of orbital irradiation (radiation induced tumours, -cataract and -retinopathy) in comparison with glucocorticoid treatment. Mortality was similar in both groups. Seventy-five per cent of the living patients participated in the follow-up study. There was no difference in cataract prevalence between irradiated and non-irradiated GO patients at follow-up, whereas there was a significant difference in the frequency of retinal changes (21% vs. 2%). These retinal changes were mostly so called background retinopathy, which is also found in 5-10% of healthy individuals. Whether this leads to proliferative retinopathy is not known, but seems unlikely. However, in five irradiated patients there was true retinopathy, clearly associated with risk factors such as diabetes mellitus or hypertension. The Relative Risk for developing retinopathy in diabetic patients treated with radiotherapy was 21. None of the diabetic patients had signs of retinopathy on fundoscopy before irradiation. Our main conclusion is that orbital irradiation seems to be safe, also in the long run, but diabetes mellitus should be considered a contraindication for orbital irradiation in GO patients.

The aim of the study described in chapter 8, was to evaluate the quality of life in patients treated for their GO on average ten years ago. These were the same patients who participated in the follow-up study described in chapter 7. From the cohort of 208 GO patients, 172 patients completed two general health-related quality-of-life (HRQL) questionnaires and the specific GO questionnaire (GO-QOL). The HRQL scores of the patients were better than those of untreated GO patients but worse than those of the reference populations of ‘healthy’ persons. The GO-QOL demonstrated that symptoms and signs of GO persist and patients keep having trouble with daily visual functioning and general physical functioning. It is concluded that GO has a marked negative effect of HRQL, even many years after treatment. Therefore our efforts should be directed not only at restoring visual function and appearance but also at patients’ coping with limitations in visual functions and psychosocial functioning.

Finally, in chapter 9 some critical remarks are made about the studies presented in this thesis. It remains difficult to find easy-to-measure reliable biological markers for the activity of the eye disease in GO patients. Serum measurements of molecules such as cytokines or adhesion molecules are probably just a weak reflection of the autoimmune process in the orbit. This explains their low positive and negative predictive value in respect to predict response to immunosuppressive intervention. Speculations about future specific immunomodulatory therapy are partly based on results from chapter 5. A management scheme for GO patients is presented based on duration of eye disease, activity and severity. General measures consist of urging all GO patients to refrain from smoking and immediate treatment of abnormal thyroid function. Future efforts should be directed at both prevention and therapeutic improvement.