ORIGINAL CONTRIBUTION

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Histological and radiological signs indicative for chronic sinus mucosal inflammation in Graves' ophthalmopathy*

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SUMMARY

Orbital decompression and, in some cases, decompression of the optic nerve are the principal surgical procedures used for treatment of moderate or severe Graves' orbitopathy (GO). Histological examination of the surgical specimens of the ethmoid revealed a wide spectrum of inflammatory mucosal changes. The charts of 68 GO patients (55 female and 13 male; age range: 14 – 85 years) were retrospectively reviewed. Lund - Mackay scores were calculated for each patient based on findings of pre-operative computer tomography (CT) sinus scans, and the incidence of histological changes associated with polypoid and eosinophilic inflammation was assessed. Files did not reveal any evidence of chronic rhinosinusitis with or without nasal polyps based on endoscopic findings. Sinus opacification on CT (of any extent) was found in 20 out of the 68 patients (29.4%). On histological exam, histological changes of the sinus mucosa indicative for chronic rhinosinusitis were found in 31 out of the 68 GO patients (45.5%). A histological examination of the sinus mucosa indicative for chronic polypoid inflammation was present in 25 patients. Fourteen out of these 25 patients showed mucosal tissue eosinophilia on histology. Six patients had mucosal changes suggesting chronic non-polypoid inflammation with tissue eosinophilia on histological exam. The incidence of chronic rhinosinusitis in individuals without GO ranges between 10 and 15%. The incidence of histological changes of the sinus mucosa indicative for chronic rhinosinusitis described in this investigation suggests that chronic inflammatory disease is considerably more frequent in GO patients, when compared to the incidence of chronic rhinosinusitis in individuals without GO. Additionally, our data underline that CT imaging of the paranasal sinuses underestimates (29.4%) the incidence of inflammatory changes of the sinus mucosa (45.5%) of any extent in GO patients.

Key words: Rhinosinusitis, Graves's disease, opthalmopathy, computed tomography, histology

INTRODUCTION

Autoimmune processes involving fibroblasts of extraocular muscles and retrobulbar fatty and connective tissues are thought to be the pathological substrate underlying Graves' ophthalmopathy (GO) [1]. Nonetheless, the nature of the causative autoantigen(s) is still unknown. The resulting changes lead to visual disturbance and cosmetic deformity. Systemic (oral and / or intravenous) steroids, non-steroidal immunosuppressants (cyclosporine), intravenous immunoglobulin [2] and external beam retrobulbar irradiation [3] are commonly the first line of treatment of GO. Some patients with moderate or severe GO do not respond to these treatment modalities and hence are candidates for surgical treatment.

Even after successful immunosuppressive therapy and / or radiotherapy, most patients have remaining (functional or cosmetic) occular changes requiring surgical therapy [4]. Orbital decompression and, in some cases, decompression of the optic nerve are the principal surgical procedures used for treatment of moderate or severe GO. Various surgical decompression techniques have been used with variable effectiveness [5-9]. Endonasal and transpalpebral orbital decompression with fat removal (with concomitant decompression of the optical nerve, if indicated) is the preferred surgical treatment of GO in our department [9].

MATERIALS AND METHODS

Study design

In this retrospective study the charts of 68 patients (55 female and 13 male; age range: 14 – 85 years) were reviewed. All patients included for analysis suffered from GO. Charts were reviewed for any documented endoscopic endonasal signs of chronic rhinosinusitis (CRS). Based on findings of pre-opera-

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tive computer tomography (CT) scans, scores based on the Lund-Mackay staging system [11] were calculated for each patient.

Histological findings

Findings on histological exams of the surgical specimens were used to assess the incidence of histological signs of inflammatory disease of the paranasal mucosa like tissue eosinophilia and polypoid changes. Histological changes of the sinus mucosa were determined to be indicative for chronic rhinosinusitis in any specimen of ethmoid cell origin if more than 5 eosinophils and / or more than 5 neutrophils were detected per HPF.

Additionally, in specimens with histological changes of the sinus mucosa suggestive of polypoid chronic inflammation, increased edema of the subepithelial stromal tissue with a clear decrease in the number of glands and concomitant epithelial damage were found. In specimens with histological changes of the sinus mucosa indicative for chronic non-polypoidinflammation, extensive stromal fibrosis without (or with minimal) subepithelial edema and goblet cell hyperplasia were observed.

Treatment

Prior to surgical therapy, all included patients had been treated with systemic steroids (oral prednisone and / or intravenous methylprednisolone) and 45 out of the 68 patients had been additionally treated with external beam irradiation therapy to the orbit using a linear accelerator to deliver a total dose of 15 to 20 Gy per orbit. The indications for surgery were decreasing visual acuity or disturbed colour vision, diplopia, increase in intraocular pressure and exophthalmus despite treatment with steroids and orbital irradiation.

All patients whose charts were included in this review had both endonasal microscopic and transpalpebral orbital decompression. Sixty-one patients had bilateral GO and were bilaterally decompressed and the remaining seven had unilateral GO and were therefore unilaterally decompressed.

Statistics

Lund – Mackey staging scores were compared between the group of patients with bilateral and the one with unilateral GO by means of the non-parametric Mann-Whitney U test with p-values less than 0.05 considered significant.

Patients undergoing revision surgery for recurrent or persistent GO as well as patients who had previously undergone surgery of the paranasal sinuses for chronic rhinosinusitis were not included for analysis in the present study.

RESULTS

Clinically, based on the endoscopic findings, none of the 68 patients included in this investigation had nasal polyps, edematous mucosal changes, pathologic secretions in the middle meatus or any other clinical signs of CRS. Patients did not complain of symptoms of chronic sinusitis before surgery, especially given that the symptoms of endocrine orbitopathy were particularly intense and dominated the clinical picture and concerns of the patients. Sinus opacification on CT (of any extent) was found in 20 out of the 68 patients (29.4%). The extent of radiographic signs indicative for CRS estimated by means of the Lund-Mackey-score is presented in Table 1. Sinus opacification on CT scan is encountered in 10.9% [12] of people without clinical symptoms of chronic sinusitis. As a result, GO patients display a considerably increased incidence of sinus opacification on CT when compared to the general population.

Table 1. Lund-Mackay scores of the 68 studied patients based on preoperative CT scan findings.

No. of patients	Lund-Mackay-score
3	24
1	16
1	12
5	8
1	6
3	4
6	2
48	0

Histological changes of the sinus mucosa were found in 31 out of the 68 GO patients (45.5%).

Histological changes of the sinus mucosa indicative for chronic polypoid sinusitis were detected in 25 patients (36.7%). Eighteen out of these 25 patients (72%) had sinus opacification on CT-scans and 14 out of these 25 patients (56%) showed markedly increased mucosal tissue eosinophilia on histologic exam. In six patients chronic non-polypoid inflammatory changes of the sinus mucosa with tissue eosinophilia were found on histological exam. Only two of them had sinus opacification on CT-scans. Twenty patients (29.4%) showed extensive mucosal fibrosis on histological exam. Lund – Mackey scores between the group of patients with unilateral and bilateral GO did not differ significantly ($p = 0.310$).

DISCUSSION

The incidence of chronic sinusitis in individuals without GO ranges between 10 and 15% [13]. According to our findings, the incidence of histological changes of the sinus mucosa indicative for chronic sinusitis is considerably increased in GO patients, compared to the incidence of chronic rhinosinusitis in individuals without GO. Interestingly, none of the patients displayed signs of chronic rhinosinusitis on nasal endoscopy, suggesting a subclinical level of inflammatory mucosal changes potentially associated with the underlying autoimmune stimuli. An earlier report from our group from 1979 already described a poor correlation between endoscopic findings and histological ones [14]. Given that a previous course of high steroid dose and / or radiation therapy have been administered prior to surgery, an improvement / normalization in the endoscopic findings may have occurred at the time of surgery.

Additionally, CT imaging of the paranasal sinuses underestimates (29.4%) the incidence of inflammatory changes of the sinus mucosa (45.5%) of any extent in GO patients.
Histologically, patients with GO have a higher incidence of inflammatory changes of the sinus mucosa when compared to individuals without GO (general population). It is difficult to suggest, based on this finding, that GO (or even Graves' disease, GD) is the causative factor of the histological changes of the sinus mucosa indicative for chronic inflammation found in GO patients. The sinonasal mucosa of these patients has not only been subjected to the autoimmune processes associated with GO and GD, but also to the external beam irradiation therapy and to the anti-thyroid medication prescribed for hyperthyroidism, at least in some patients.

In patients with autoimmune disorders, vasculitic and non-vasculitic mucosal changes without the typical histological hallmarks of the immune vasculitis are encountered [15]. Patients with GO are first treated with immunosuppressive agents, then subjected to low dose irradiation followed by new course(s) of immunosuppression (steroids) and only after failure of these measures undergo surgery. As a result mucosal inflammation at the time of surgery would rather be suppressed [16,17]. During the active phase of the disease the degree and possibly even the incidence of chronic inflammation would expectedly be higher than at the time of surgery.

Whereas irradiation with high doses is established to exert pro-inflammatory effects, low dose radiotherapy with single fractions below 1.0 Gy has confirmed anti-inflammatory effects not only clinically but also seen in in vivo and in vitro models [16]. Clinically this seems also to be the case when limiting total irradiation dose to 15-20 Gy with small single doses over a time period of weeks, as done in our patients. As the irradiation is performed using head mask fixation, individual lead shielding and parallel opposed linear accelerator fields for orbital irradiation of Graves's orbitopathy, doses reaching the sinus mucosa are rather low, following the consensus guidelines for radiation therapy of benign diseases.
It would be interesting to see, if inflammatory changes of the mucosa at the roof of the maxillary sinus or the medial wall of the ethmoid complex are different from changes at greater distance from the irradiation field, however this is beyond of the scope of the present publication.
Furthermore, an increased incidence of postoperative purulent sinusitis was observed after orbital decompression in our series [18]. Therefore patients with GO should be preoperatively informed about the possible necessity of a more extended sinus procedure to clear concomitant sinus disease as well as about an increased likelihood of developing purulent sinusitis postoperatively. In patients in whom CT scan involvement of the sinuses other than the ethmoid was present, additional (more extensive) sinus surgery including the respective sinuses was performed. Additionally, postoperative endonasal patient care was more intensive in patients with more extensive surgery and abnormal findings on histology.
Despite the previous application of systemic steroids, a high incidence of histological chronic inflammatory changes of the sinus mucosa was noted. It could be that without the previous use of steroids, the incidence of histological changes of the sinus mucosa indicative for chronic inflammation would have been even higher. To further elucidate the latter issue, one should (in addition to a detailed history taking and a thorough endoscopic nasal examination) perform CT scans of the sinuses and, when possible, take biopsies of endonasal tissue (given that, according to the present study, CT scans underestimate the incidence of histological changes of the sinus mucosa indicative for chronic inflammation) before starting immunosuppressive (steroid) treatment in GO patients.
The question about possible decompression surgery arises after completion of medical or radiation treatment. This is the reason why CT scans are usually performed at that time and hence are likely to miss the possible existence of more extensive sinus findings.
We do not advocate that one should consider findings on CT scans as diagnostic of the clinical entity of chronic sinusitis. Nonetheless, any histological changes of the sinus mucosa indicative for chronic inflammation should be considered as serious evidence for the actual existence of chronic rhinosinusitis in the respective patients.

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