Concise report

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Disease-related burden and long-term outcome in orofacial granulomatosis: observations from a large single-centre cohort

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Summary

There is a lack of standardized treatment recommendations for orofacial granulomatosis, a chronic inflammatory condition aetiologically related to Crohn disease. To assess clinical baseline parameters and treatment strategies, we retrospectively analysed 61 consecutive cases from our institutional database. Disease-related functional/psychological impairment and long-term outcomes were descriptively evaluated using a standardized self-reporting questionnaire. The median age of patients was 45 (7–77) years. Oral steroids were given in 41.0% of cases, but only produced short-term disease control, while response to steroid-sparing agents was inconsistent. Only a minority of patients reported relevant disease-related functional impairment in eating (21.7%) or speaking (4.3%), but the majority perceived psychological distress due to the cosmetic aspects of the disease (69.6%), comments from others (65.2%) and/or general anxiety/insecurity (73.9%). Regardless of the initial treatment, long-term outcomes after 71 months (range 7–304 months) were beneficial, with most patients being in complete remission (52.2%) or reporting only mild residual swelling (43.5%).

Orofacial granulomatosis (OFG) is a chronic inflammatory condition that is clinically characterized by persistent swelling of the orofacial soft tissues.[1–3] It is aetiologically related to Crohn disease (CD).[1–3] Histology, typically reveals noncaseating granulomas; however, these may be difficult to locate in small biopsies.[4] The associated triad of granulomatous cheilitis, peripheral facial palsy and plicated tongue is referred to as Melkersson–Rosenthal syndrome (MRS). Although numerous treatment options have been described in case reports and small series,[1–3,5,6] there is a lack of standardized treatment recommendations and long-term observational data. We performed a study aiming to (i) characterize clinical baseline parameters in a large cohort of patients, (ii) assess disease-related functional and psychological impairment, and (iii) evaluate treatment strategies and long-term outcomes.

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Report

Approval for the study was obtained from the ethics committee of the Medical Faculty, University of Würzburg and all patients answering the questionnaire provided informed consent.

The institutional database was searched using the International Classification of Diseases, Version 10 codes K13.0, K13.4, K13.7, L92.8, L92.9 and G51.2. Individual examination of 554 patient files over the period 2004–2019 identified 61 cases of OFG based on history, clinical findings (persistent swelling of the orofacial soft tissues in the absence of trauma, chronic infection, or other specific cause) and histology where available. Retrospective data evaluation included age, sex, clinical manifestations of OFG, histology, comorbidity and treatment. A subgroup of 42 patients with complete documentation of at least two follow-up visits was asked to provide additional information on

individual disease-related functional and psychological impairment and long-term outcomes using a standardized questionnaire (Supplementary Data S1).

In the total group of 61 patients, the median age was 45 years (range 7–77 years) and the sex ratio was balanced (Table 1).

The majority of patients had granulomatous cheilitis (n = 58; 95.1%) predominantly involving the upper lip. Of the 61 patients, 11 (18.0%) reported one or several episodes of peripheral facial palsy, while only 5 (8.2%) presented the complete triad of MRS. Regarding comorbidities, chronic inflammatory bowel disease was present in 10 patients (16.4%) and concurrent diabetes in 9 (14.8%).

The median observation time from the first to the final visit was 7 months (range 0–194 months). Of the 61 patients, 20 (32.8%) had not received any specific treatment, while 25 (41.0%) had been treated with oral prednisolone and 6 (9.8%) had been treated with intravenous dexamethasone pulses. An improvement (68.0%) or even complete remission (12.0%) under steroid treatment was documented in most cases, but relapses upon tapering of the steroid were common. The most frequently used steroid-sparing agents were sulfasalazine (18 cases) and clofazimine (16 cases); the tolerability of both substances was good, but the therapeutic response was inconsistent. Other treatments included dapsone (n = 5), azathioprine (n = 2), hydroxychloroquine (n = 2) and methotrexate (n = 1). Two patients with concurrent CD were treated with infliximab and both showed an excellent response.

Table 1 Clinical baseline parameters and treatment in 61 patients with orofacial granulomatosis.

Parameter	
Age at first presentation, years[a]	45 (7–77)
Age groups, *n* (%)	
Children/adolescents, < 18 years	4 (6.6)
Young adults, 18–29 years	11 (18.0)
Female sex	31 (50.8)
Clinical manifestations of OFG, *n* (%)	
Cheilitis	
Upper and/or lower lip	58 (95.1)
Upper lip	48 (78.7)
Lower lip	28 (45.9)
Pareiitis (cheeks)	24 (39.3)
Plicated tongue	16 (26.2)
Facial palsy	11 (18.0)
Full triad of MRS	5 (8.2)
Histology,[b] *n* (%)	
Granulomatous inflammation	32 (65.3)
Nonspecific	17 (34.7)
Comorbidity, *n* (%)	
Chronic IBD	10 (16.4)
Diabetes	9 (14.8)
Sarcoidosis	0 (0.0)
Treatment,[c] *n* (%)	
No specific treatment (watch and wait)	20 (32.8)
Oral prednisolone	25 (41.0)
IV dexamethasone pulse therapy	6 (9.8)
Sulfasalazine	18 (29.5)
Clofazimine	16 (26.2)
Dapsone	5 (8.2)

IBD, inflammatory bowel disease; IV, intravenous; MRS, Melkersson–Rosenthal syndrome; OFG, orofacial granulomatosis. [a]Median (range). [b]Available in 49 cases (80.3%). [c]Additional treatments included infliximab (n = 2), azathioprine (n = 2), hydroxychloroquine (n = 2) and methotrexate (n = 1).

Complete questionnaires were available from 23 patients (11 women, 12 men). Referring to the time of maximum disease activity, relatively few patients reported relevant (moderate to severe) impairment due to difficulties in eating (n = 5, 21.7%) or speaking (n = 1; 4.3%) (Fig. 1a). However, 16 (69.6%) patients reported relevant psychological distress due to cosmetic aspects, 15 (65.2%) due to comments from other people and 17 (73.9%) due to general anxiety/insecurity (Fig. 1b).

The median time interval from first presentation to questionnaire-based data collection was 71 months (range 7–304 months). Of the 23 patients, 20 (87.0%) had received treatment initially, but only 4 (17.4%) were receiving ongoing active treatment at the time of data collection. Five (21.7%) patients reported episodes of acute swelling within the last 12 months (Fig. 1c). Twelve patients (52.2%) were in complete remission and a further 10 (43.5%) had only mild residual swelling (Fig. 1d).

In this study, our patients' median age of 45 years is in accordance with recent observations from other groups,[1,2,5,7] but is in contrast to the doctrine saying that OFG predominantly affects young adults.[3] Our finding of coexisting OFG and diabetes is suggestive of a possible association.[8] The median age in the diabetic subgroup was 63 years (range 31–73 years), suggesting that Type 2 diabetes might be a risk factor for late onset OFG, a hypothesis that needs to be confirmed in larger studies.

Our study data confirm granulomatous cheilitis affecting the upper lip as the most frequent manifestation of OFG.[1–3,7] The full MRS triad was found in only five (8.2%) patients, which is close to the even lower rate of 2.76% reported in a recent systematic review.[3] More than twice as many patients (18.0%) reported one or several episodes of peripheral facial palsy, but not all fulfilled the criteria for MRS due to the absence

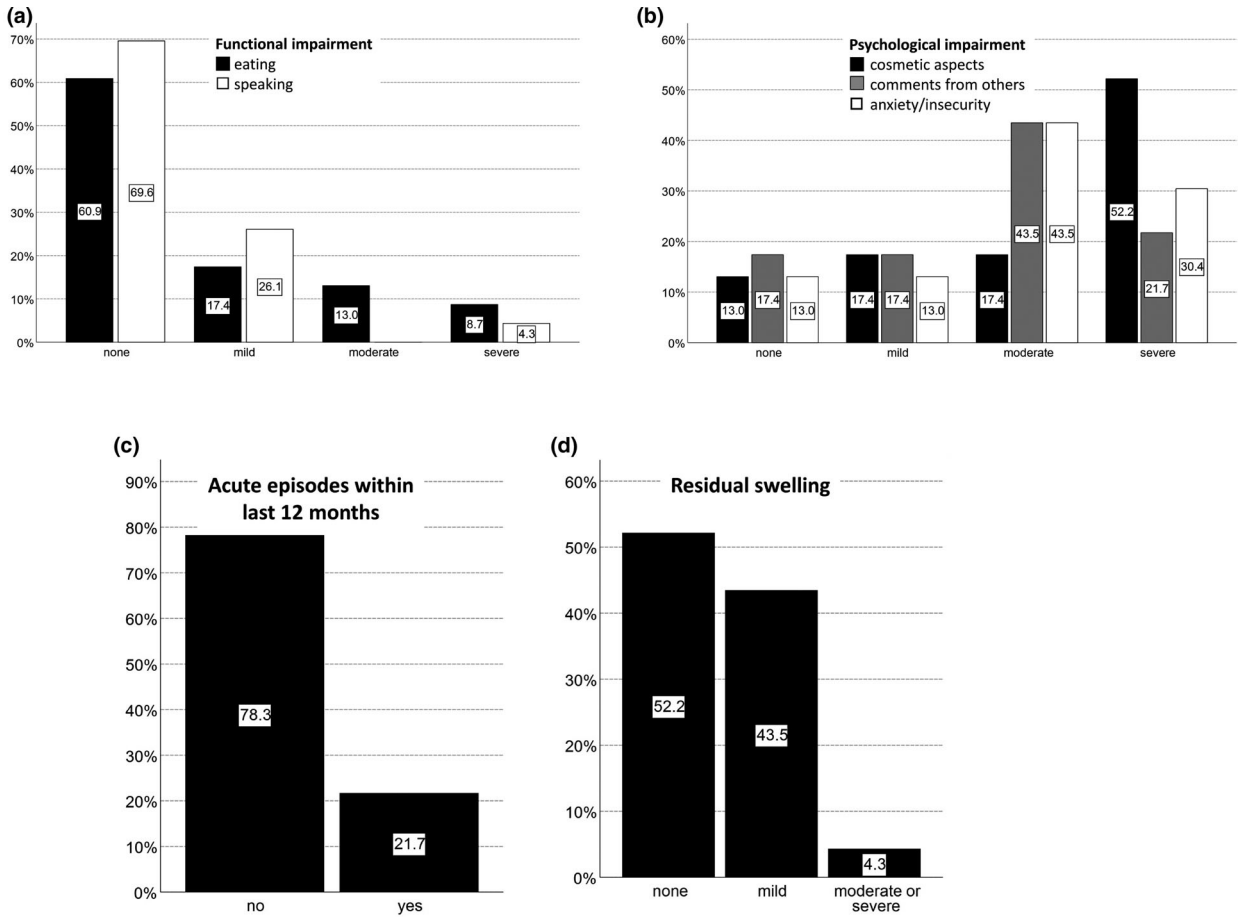

Figure 1 (a–d) Disease-related (a) functional and (b) psychological impairment and long-term outcomes of patients with orofacial granulomatosis after a median of 71 months regarding (c) acute episodes and (d) residual swelling/deformation according to questionnaire-based self-reporting.

of cheilitis ($n = 1$) or plicated tongue ($n = 5$). Given that plicated tongue is both asymptomatic and widespread in the normal population, we suggest that the clinical focus should be on the combination of OFG and facial palsy rather than on the classic MRS triad.

The therapeutic substances used in our series correspond to the spectrum reported in the medical literature.[1,2,5,6] Systemic steroids reliably induced short-term remission,[1,5] but the symptoms almost invariably relapsed upon tapering. Evidence supporting the use of specific steroid-sparing agents is scarce. Case series suggest a beneficial effect of tumour necrosis factor-α inhibitors,[6] which are expensive and are unapproved for the treatment of OFG, but represent a promising option whenever coexisting CD permits on-label treatment.

Our data demonstrate an overall high disease-related psychological burden, whereas functional impairment was usually mild or even absent. Prospective studies are required to quantify the OFG-related impact on quality of life; a validated questionnaire for patients with chronic oral mucosal diseases is available.[9]

Our study's main finding is the overall beneficial long-term outcome after a median follow-up period of 71 months with only mild or no residual swelling in 95.7% of cases. The long-term prospect of complete healing, which may occur independently of the initial medical treatment,[5,10] is likely to alleviate disease-related psychological distress and should be communicated to patients in the early course of OFG. Concerted efforts should be made to develop a standardized, cross-centre treatment approach to OFG (a proposal is drafted in Fig. 2).

Our study's main strengths lie in the hitherto unique evaluation of the OFG-related functional and

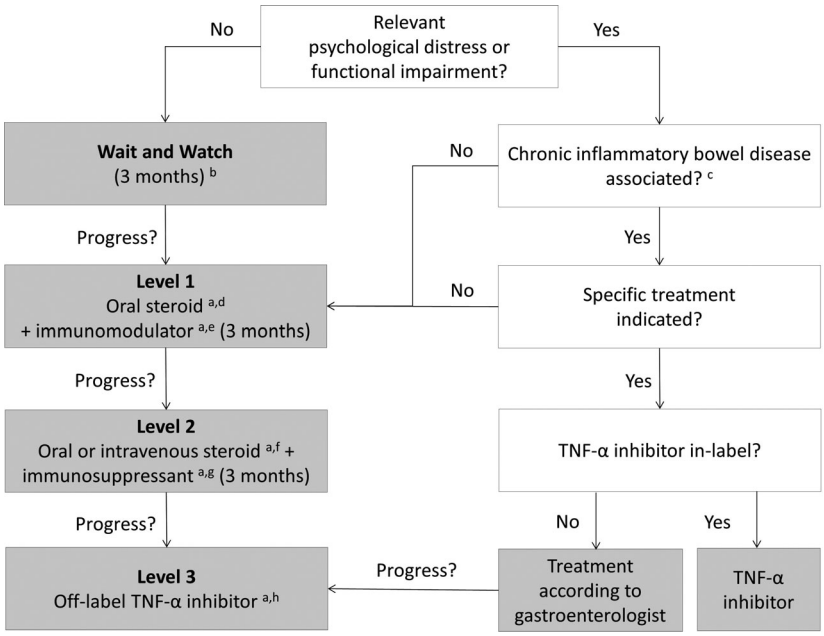

Figure 2 Proposal for standardized treatment escalation taking into account disease severity, psychological distress, comorbidity and dynamic course of orofacial granulomatosis. [a]Recommendations for the selection and dosage of medication represent the personal suggestion by the authors. Please also consult respective prescribing information. [b]Provide instructions on standard mouth hygiene; dental consultation should be considered in cases of odontogenic infection.[7] [c]Consultation with a gastroenterologist should be considered in cases with negative history but suggestive symptoms (e.g. abdominal pain, weight loss, diarrhoea) and/or laboratory abnormalities (e.g. anaemia, hypalbuminaemia, increase in C-reactive protein, increase in faecal calprotectin). [d]For example, prednisolone at an initial dose of 1 mg/kg bodyweight (bw) per day, tapering over 4 weeks. [e]For example, sulfasalazine incremental dosing, maximum 3 g per day, hydroxychloroquine maximum 6.5 mg/kg bw per day, or dapsone 1–1.5 mg/kg bw per day.[f] For example, monthly intravenous dexamethasone pulses of 100 mg on three consecutive days. [g]For example, azathioprine 1–1.5 mg/kg bw per day or methotrexate 10–20 mg per week. [h]For example, infliximab 5 mg/kg bw at weeks 0, 2 and 6, then every 8 weeks (cost coverage by health insurance needs to be ensured). TNF, tumour necrosis factor.

psychological burden and the extended observation period. A limitation is that the retrospective approach and limited case number allowed only for descriptive data evaluation.

Learning points

- OFG may manifest throughout lifetime and is not restricted to children and young adults.
- Type 2 diabetes might represent a risk factor for late-onset OFG.
- The combination of OFG and peripheral facial palsy frequently manifests without concurrent plicated tongue.
- Although relevant functional impairment is rare, OFG is associated with considerable psychological distress.
- Systemic steroid treatment reliably induces short-term remission, but symptoms generally relapse upon tapering.
- Long-term outcomes after a median of 71 months are overall beneficial regardless of the initial treatment.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Patient questionnaire.