Clin Oral Invest (2013) 17:1995–2002
DOI 10.1007/s00784-012-0905-z

ORIGINAL ARTICLE

Clinical characteristics of Mikulicz's disease as an IgG4-related disease

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Received: 12 May 2012 / Accepted: 3 December 2012 / Published online: 16 December 2012

Abstract
Objectives Mikulicz's disease (MD) was considered to be a subtype of Sjögren's syndrome (SS), based on histopathological similarities. However, recent studies have indicated that patients with MD show high serum IgG4 concentration, and suggested that MD is one of "IgG4-related disease" and distinguishable from SS. Therefore, we clinically and histopathologically examined the disease states of MD and SS in detail.
Materials and methods Twenty patients with Mikulicz's disease and 18 with SS were comparatively studied to determine clinical characteristics in MD patients.
Results Sialography in MD patients did not show the "apple-tree sign" typically seen in SS. Serologically, high serum IgG4 levels but not anti-SS-A or anti-SS-B antibodies were observed in MD. SS showed lymphocytic infiltration of various subsets with atrophy or severe destruction of the acini, while MD showed selective infiltration of IgG4+ plasma cells with hyperplastic germinal centers and mild acini destruction. Corticosteroid treatment of MD reduced IgG and IgG4 levels and improved salivary function. A negative correlation between disease duration and increasing rate of salivary flow was observed in MD.
Conclusions These results suggested that the pathogenesis of MD might be different from those of SS. Clinical Relevance: early diagnosis and treatment of MD is important for the improvement of salivary function.

Keywords Mikulicz's disease · Sjögren's syndrome · IgG4-related disease

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Introduction

Mikulicz's disease (MD) is a unique condition characterized by enlargement of the lacrimal and salivary glands caused by infiltration of lymphocytes. As MD and Sjögren's syndrome (SS) have histopathological similarities, MD has been considered a subtype of SS [1]. However, MD has a number of differences compared with typical SS including: (1) persistent enlargement of lacrimal and salivary glands; (2) normal or moderate salivary secretion dysfunction; (3) good responsiveness to corticosteroid treatment; and (4) hypergammaglobulinemia and low frequencies of anti-SS-A and anti-SS-B antibodies by serological analyses. MD patients show elevated levels of serum IgG4 and infiltrating IgG4-positive plasma cells in the gland tissues [2–4], and these symptoms have also been identified with other diseases such as autoimmune pancreatitis (AIP) [5], sclerosing cholangitis (SC) [6], tubulointerstitial nephritis [7], interstitial pneumonia [8], Riedel's thyroiditis [9], and Küttner's

tumor [10]. These diseases are now called "IgG4-related disease (IgG4-RD)" [4, 11–13]. In addition, we recently described the concept of IgG4-RD and reviewed information regarding this emerging disease entity [12]

Our previous immunological analyses of MD patients demonstrated that the cytokine profile and lymphocyte subsets in salivary glands differed from patients with SS. Consequently, MD is now thought of as a unique inflammatory disorder characterized by Th2 and regulatory immune reactions, which might play key roles in IgG4 production [14, 15]. Although MD is clinically and immunologically distinguishable from SS and thought to be a new clinical entity, many points remain to be elucidated. Particularly, MD patients have a high risk of relapse after steroid therapy. Serial clinical assessment including the effect of treatments on disease parameters has not yet been performed. Therefore, the aim of this study was to determine the clinical and histopathological characteristics of MD compared with SS, and to identify factors associated with the effects of corticosteroid treatment.

Patients and methods

Patients

Twenty patients with MD (14 women and 6 men, mean age 60.1±12.1 years) and 18 patients with SS (16 women and 2 men, mean age 54.6±12.8 years), referred to the Department of Oral and Maxillofacial Surgery, Kyushu University Hospital between April 1993 and December 2010, were included in the study. MD was diagnosed according to the following criteria [2]: (1) persistent (longer than 3 months) symmetrical swelling of more than two lacrimal and major salivary glands; (2) raised serum levels of IgG4 (>135 mg/dl); and (3) infiltration of IgG4-positive plasma cells in the tissue (IgG4+ cells/IgG+cells>50 %) by immunostaining. For a positive MD diagnosis, any two of the 3 items must be present including item (1). SS was diagnosed according to both the Research Committee on SS of the Ministry of Health and Welfare of the Japanese Government [16] and the American–European Consensus Group criteria for SS [17]. Each patient exhibited objective evidence of salivary gland involvement based on the presence of subjective xerostomia and a decreased salivary flow rate, abnormal findings on parotid sialography, and focal lymphocytic infiltrates in the labial salivary glands (LSGs) and submandibular glands. All patients with SS were diagnosed as primary SS with strong lymphocytic infiltration in the LSGs and no other autoimmune diseases present, and were not being treated with corticosteroids or other immunosuppressants. LSG biopsies were performed as described by Greenspan et al. [18]. This study design was approved by the Ethics Committee of Kyushu University, Japan, and informed consent was signed by the patients.

Clinical findings

The location and duration of persistent bilateral swelling, general symptoms, and the presence of dryness of mouth and eyes was examined as clinical findings. The disease duration was defined as the period from the initial observation of glandular swelling to the first visit. All patients underwent gum tests and/or Saxon tests for the objective assessment of mouth dryness. When patients had dry eyes, the Schirmer's test was used for objective assessment. Normal values for the gum test and the Saxon test are 10 ml/10 min, and 2 g/2 min, respectively. Normal values for the Schirmer's test are 10 mm/5 min, and a value of 5 mm/5 min is diagnosed as dry eye. Finally, we examined the changes in IgG subclasses and the amount of salivary secretion in the patients with MD before and after corticosteroid treatment. The starting dose of prednisolone was 0.6 mg/kg/day for 1 month and decreased to 5–10 mg/day every 2 weeks (mean duration of treatment: 12.4±6.7 months, maintenance dose 5–7.5 mg/day). In this analysis, clinical remission was defined as no observation of glandular swelling at least 3 months as determined by physical and imaging findings.

Serologic examinations

Serologic analysis was performed for rheumatoid factor (RF), antinuclear antibody (ANA), IgG, IgG4, IgA, IgM, anti-SS-A, and anti-SS-B antibodies. Normal values were as follows: RF, <20 IU/mL; IgG, 872–1,815 mg/dL; IgG4, 4.8–135 mg/dL; IgA, 95–405 mg/dL; and IgM, 59–269 mg/dL. Levels of ANA were divided into four grades: negative, >40 units; 1+, 40–160 units; 2+, 160–640 units; and 3+, <640 units. Anti-SS-A and anti-SS-B antibodies were evaluated as positive when minute amounts were detected by enzyme-linked immunosorbent assay.

Sialographic examinations

Sialography was performed with a water-soluble contrast medium, amidotrizoate 76 % (Urografin 76 %; Schering-Japan, Osaka, Japan). Sialographic images were evaluated by a single observer (M.S.), based on the classifications by Rubin and Holt [19] as follows: normal, no abnormal dilation of the peripheral ducts; stage I (punctate), diffuse punctate dilation of the peripheral ducts by 1 mm; stage II (globular), the globules of contrast material increase to 1–2 mm; stage III (cavitary), the globules become irregular in size and distribution with cystic dilation; and stage IV (destructive), destruction of the gland parenchyma.

Histological study of LSGs

Four-micrometer formalin-fixed and paraffin-embedded sections of LSGs specimens were prepared and stained with

Table 1 Clinical characteristics of 20 Mikulicz's disease (MD) patients

No.	Age	Sex	Disease duration	Complications	Swollen glands						Complaint		Gum test (g/10min)	Schirmer's test (R/L) mm/5 min	Serological test							
					LG	PG	SMG	SLG	PLG	LSG	Dry mouth	Dry eyes			RF (IU/ml)	ANA	IgG (mg/dl)	IgG4 (mg/dl)	IgA (mg/dl)	IgM (mg/dl)	Anti-SS A	Anti-SS-B
1	70	M	6 M	Asthma	–	O	O	–	–	–	O	O	1.0	1/1	20>	–	2010*	ND	390	222	–	–
2	48	F	3 M	Asthma	O	–	–	–	–	O	O	O	4.0	8/4	20>	1+*	2401*	ND	161	85	–	–
3	31	F	1Y6M	AIP,DM	O	O	–	O	–	–	O	–	8.0	ND	20>	1+*	2055*	ND	184	36	–	–
4	68	F	3 M	AIP,DM	O	–	O	O	–	–	O	–	13.0	ND	20>	–	2827*	ND	290	91	–	–
5	52	F	3Y	Breast cancer	O	–	O	O	O	O	O	–	7.8	ND	20>	2+*	3191*	ND	179	142	–	–
6	37	F	20Y	–	O	O	O	–	–	–	O	O	14.0	4/9	65*	3+*	1443	ND	285	111	–	–
7	66	M	2Y	Prostate hypertropy	–	–	O	O	–	–	–	–	16.0	ND	ND	ND	ND	ND	ND	ND	–	–
8	65	M	5 M	Hydronephrosis	–	–	O	–	–	O	–	–	12.0	ND	20>	–	3142*	1700*	138	59	–	–
9	57	F	6 M	AIP,SC	O	–	O	–	–	–	–	–	9.8	3/3	20>	–	1842*	748*	187	63	–	–
10	61	F	3 M	AIP,SC	–	–	O	–	–	O	O	O	6.3	3/1	ND	–	2891*	1080*	187	63	–	–
11	64	F	1Y	AIP	–	O	O	–	–	–	O	O	ND	ND	61*	2+*	2585*	456*	305	53	–	–
12	79	F	10Y	AIP,SC	–	O	O	–	–	–	O	O	ND	ND	20>	–	2430*	896*	182	53	–	–
13	60	F	1 Y	AIP,SC	–	–	O	–	–	–	O	O	11.6	ND	20>	–	2087*	490*	276	74	–	–
14	70	F	5 Y	–	–	O	–	O	O	O	O	O	11.1	ND	20>	–	5408*	1930*	148	89		–
15	76	F	4 M	DM	–	O	O	–	–	–	O	O	5.3	4/9	ND	–	2381*	823*	187	52	–	–
16	79	F	3 M	–	–	O	O	–	–	–	–	–	ND	ND	20>	–	2608*	896*	132	68	–	–
17	46	F	6 M	Chronic thyroiditis	O	–	O	O	O	O	–	–	8.1	ND	20>	–	2200*	769*	244	78	–	–
18	66	M	5Y	–	O	–	O	–	–	–	–	–	17.2	3/3	20>	–	2121*	344*	167	45	–	–
19	61	M	3Y	Pulmomary nodules	O	O	O	O	–	–	O	–	6.8	3/1	20>	–	7603*	2290*	121	62	–	–
20	61	M	2Y	Asthma	O	–	–	O	–	–	–	–	12.5	ND	20>	–	2728*	590*	223	54	–	–

AIP autoimmune pancreatitis, *SC* sclerosing cholangitis, *DM* diabetes mellitus, *LG* lacrimal gland, *PG* parotid gland, *SMG* submandibular gland, *SLG* sublingual gland, *PLG* palatal gland, *LSG* labial salivary gland, *ND* not done, – negative

*higher than normal values

haematoxylin and eosin (HE) for conventional histological examinations. The degree of lymphocytic infiltration in the specimens was graded from 0 to 4 using the scale reported by Chisholm and Mason [20]. In this study, HE-stained LSG tissue sections from 20 patients with MD and 66 patients with primary SS who were referred to the Department of Oral and Maxillofacial Surgery, Kyushu University Hospital between 1993 and 2011 were evaluated for the frequency of ectopic GC formations.

Immunohistochemical analysis of LSGs

For the immunohistochemical analysis of lymphocyte subsets, 4-μm formalin-fixed and paraffin-embedded sections were prepared and stained using a conventional avidin–biotin complex technique as reported previously [21]. The mouse monoclonal antibody used to analyze IgG4+ plasma cells was anti-IgG4 (The Binding Site, Birmingham, UK). The sections were sequentially incubated with primary antibodies, biotinylated anti-mouse IgG secondary antibodies (Vector Laboratories, Burlingame, CA), avidin–biotin horseradish peroxidase complex (Vector Laboratories), and 3,3′-diaminobenzidine (Vector Laboratories). Mayer's hematoxylin was used for counterstaining. Photomicrographs were obtained using a light microscope equipped with a digital camera (CoolSNAP; Photometrics, Tucson, AZ).

Statistical analysis

The statistical significance of the differences between the groups was determined using Student's *t* test, Fisher's exact test, and Pearson's product–moment correlation. All statistical analyses in this study were performed using JMP software (version 8; SAS Institute, Japan). A *p* value of less than 0.05 was considered statistically significant.

Results

Clinical findings

Table 1 shows the clinical characteristics of the 20 cases of MD. All cases showed bilateral swelling of lacrimal or salivary glands over the course of 3 months. Six cases suffered from dryness of mouth. However, only 50 % of patients showed an objective decrease of saliva flow in both gum and Saxon tests. The mean values of the gum and Saxon tests from nine cases were 9.6 ml/10 min and 2.97 g/2 min, respectively. These results suggest that the decrease of saliva flow was relatively mild in MD. Frequent complications of MD included AIP (seven cases), SC (four cases), asthma (three cases), and diabetes mellitus (three cases). As shown Table 2, all of the patients with MD developed high serum IgG and IgG4 levels (the IgG4 test was performed in 13 cases). In contrast, all cases were negative for anti-SS-A and anti-SS-B antibodies. Serum IgA and IgM levels were within normal limits.

Sialographic findings

Representative sialographic findings in the salivary glands from MD and SS patients are shown in Fig. 1. Except in one case with ductal dilation, 19 of 20 cases showed normal parotid gland sialograms. No MD patients showed punctate or globular patterns. In addition, sialography of submandibular glands with the existence of swelling did not show the "apple-tree sign", which is characteristic of SS, although parenchymal defects in glandular images were observed in accordance with the nodal areas.

Histological findings in the LSGs

Representative histological findings in the LSGs specimens from MD and SS patients are shown in Fig. 2. SS patients

Table 2 Comparison of frequencies of clinical and laboratory findings between MD and severe Sjögren's syndrome

		SS	MD
Decreased salivary flow by Gum test		100.0 %(18/18)*	52.9 %(9/17)
<mean±S.D., ml/10 min>		<4.9±2.5>	<9.7±4.3†>
Glandular swelling		11.1 %(2/18)	100.0 %(20/20)*
Sialography (Rubin & Holt)	stage 0	0.0 %(0/18)	100.0 %(20/20)
	stage I	5.6 % (1/18)	0.0 %(0/20)
	stage II	44.4 %(8/18)	0.0 %(0/20)
	stage III	50.0 %(9/18)	0.0 %(0/20)
Infiltration of $IgM4^+$ plasma cells[a]		0.0 %(0/18)	100.0 %(20/20)*
Elevation of serum IgG		68.8 %(11/16)	94.7 %(18/19)
Detection of IgG4		ND	100.0 %(13/13)
ANA		100.0 % (16/16)*	26.3 %(5/19)
Anti-SS-A		88.9 % (16/18)*	0.0 % (0/20)
Anti-SS-B		50.0 % (9/18)*	0.0 % (0/20)

Positive rates (frequencies of patients with abnormal findings) are shown

†$p<0.05$ (Student's *t* test), *$p<0.05$ (Fisher's test)

[a]IgG4+ plasma cells/IgG + plasma cells >50 %

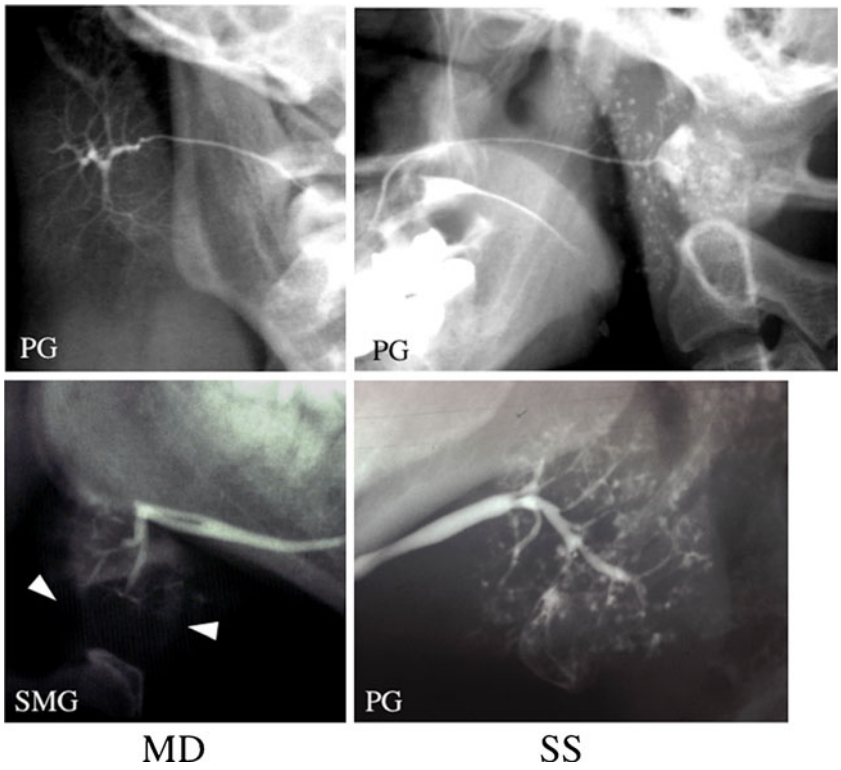

Fig. 1 Sialographic findings of Mikulicz's disease (*MD*) and Sjögren's syndrome (*SS*). *Arrowheads* contrast defect. *PG* parotid gland, *SMG* submandibular gland

showed periductal lymphocytic infiltration with atrophy and/or severe destruction of the acini, and a very small number of IgG4+ plasma cells. In contrast, MD patients showed selective infiltration of IgG4+ plasma cells with hyperplastic germinal centers (GCs) and mild destruction of the acini in comparison to SS. In this study, HE-stained LSG tissue sections from 20 MD patients and 66 primary SS patients were evaluated and screened for the ectopic GC formation. As a result, 12 MD patients (60.0 %) and 15 primary SS patients (22.7 %) were found to have the ectopic GC formation (manuscript in preparation).

Changes in clinical findings following corticosteroid treatment

Figure 3 shows the changes in total serum IgG and IgG4 following steroid therapy in MD patients. Both total IgG and IgG4 levels significantly decreased following treatment (mean treatment period 101.6±61.4 days). The values of

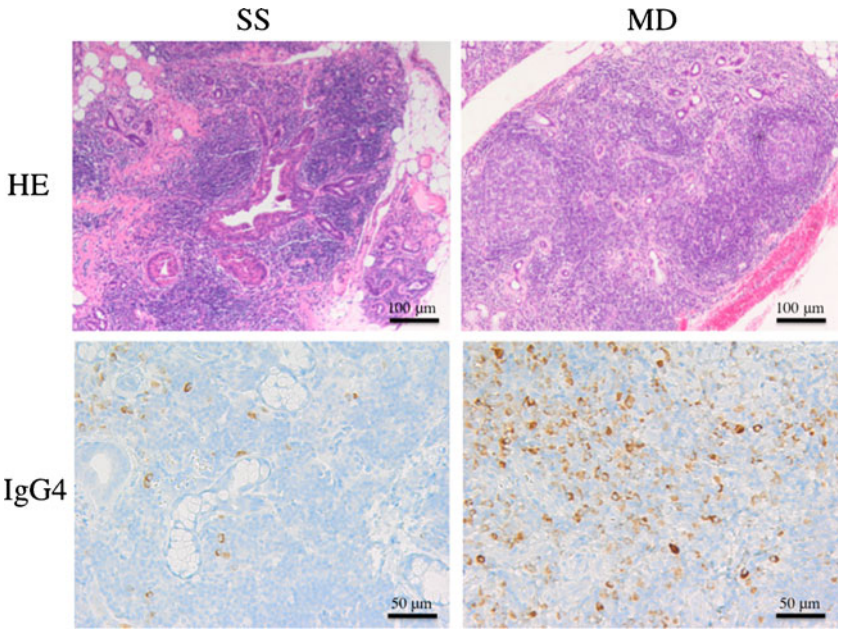

Fig. 2 Histological findings in the labial salivary glands of MD and SS

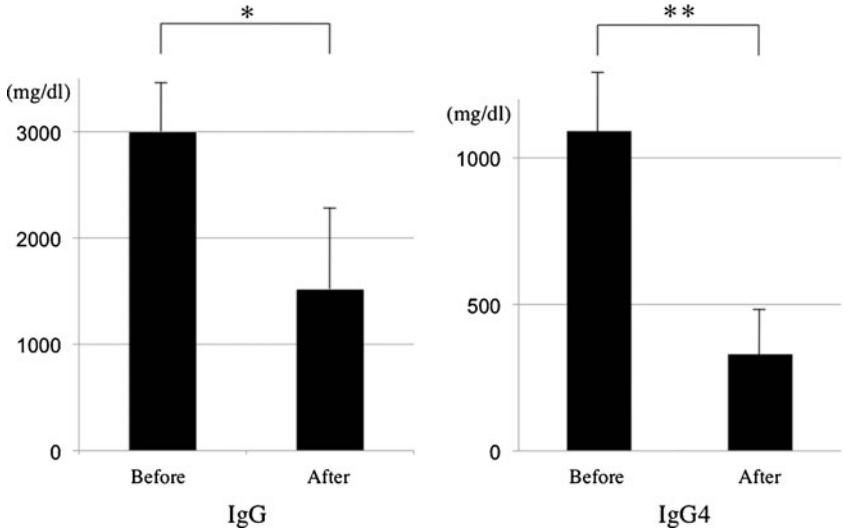

Fig. 3 Changes in total serum IgG and IgG4 after corticosteroid treatment in MD patients *$p<0.05$, **$p<0.01$ (Student's t test) compared with levels before corticosteroid treatment

IgG4/total IgG percentage before and after steroid treatment were 32.14±10.32 % and 18.41±11.21 %, respectively.

Relationship between post-therapy improvement of salivary function and clinical findings

The relationships between the rate of increase in saliva and swelling duration of salivary glands were examined. Salivary function was either improved or normal upon steroid administration. The increasing ratio of salivary function was negatively correlated with disease duration (Fig. 4), while was not correlated with the decreasing ratio of total IgG, IgG4, and IgG4/total IgG percentage (data not shown).

Discussion

MD presents with bilateral and persistent swelling of the lacrimal and salivary glands, and since the findings of Morgan and Castleman were published in 1953, has been considered to be part of primary SS or a subtype of primary SS [1]. However, Yamamoto et al. reported differences in the clinical and histopathological findings between MD and SS [2–4]. Serologically, MD patients show hypergammaglobulinemia, hypocomplementemia (complement deficiency), and high levels of serum IgG4, but are negative for anti-SS-A and anti-SS-B antibodies. MD was immunohistologically detected the selective infiltration of IgG4+ plasma cells, which was not observed near acinar and ductal cells. However, similar specimens from SS patients show no IgG4 + plasma cells. In the current study, MD patients presented with non-periductal lymphocytic infiltration with hyperplastic GCs and mild destruction of the acini, while SS was characterized by periductal lymphocytic infiltration with atrophy or severe destruction of the acini (Fig. 1). Our results are consistent with the previous histological findings for MD.

Yamamoto et al. reported that salivary function in MD significantly improved after steroid therapy, whereas SS is

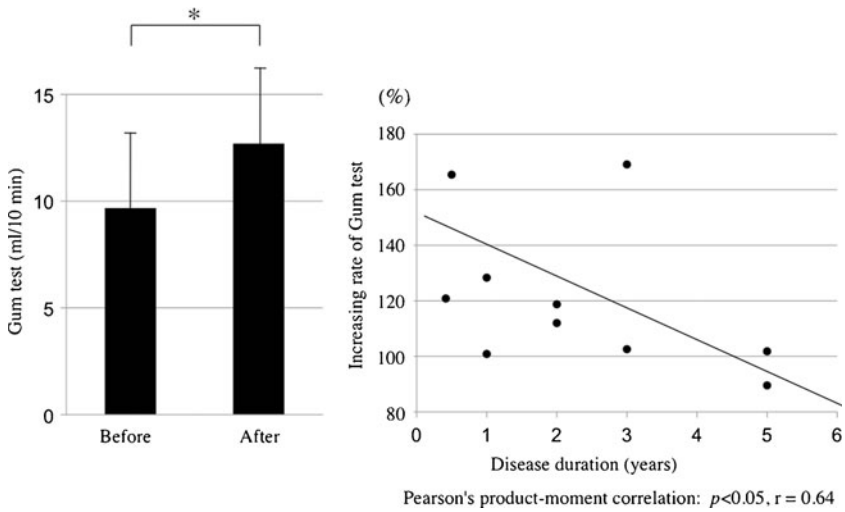

Fig. 4 Changes in salivary function after corticosteroid treatment in MD *$p<0.05$ (Student's t test) compared with levels before corticosteroid treatment

considered refractive to corticosteroid therapy [2–4]. In this study, MD patients responded well to steroid therapy and confirmed a tendency for decreased swelling of the glands immediately after the start of steroid treatment. However, the dosage and duration of the treatment remain to be established. Therefore, further studies of MD patients using higher numbers are required to clarify the long-term course of treatment. A variety of mechanisms may account for the clinical improvement in MD following steroid treatment. First, lymphocyte infiltration and function are suppressed by glucocorticoids. Second, in the setting of steroid treatment, the ability of stem cells in the ductal epithelium to promote acinar cell regeneration may be augmented. And third, probably as a result of the other two processes, salivary secretion by the acini is increased substantially. The ability of the salivary glands to respond to steroid treatment may decrease with time. Periods of longer disease duration are often associated with marked salivary gland fibrosis and the loss of acinar cells' ability to regenerate.

In conclusion, MD has similar characteristics to SS in terms of the organs affected, but has clinical (symptoms, complications, immunological data including autoantibodies and immunoglobulin class/subclasses) and histological differences. It is thought that the pathological condition of MD could be diagnosed quickly and simply using diagnostic criteria such as serum IgG4 values and the presence of IgG4+ cells in salivary glands, in conjunction with salivary-gland imaging, sonography, and CT scans. In addition, our previous reports suggest that sonography could be used to distinguish MD from SS and should be recommended as a follow-up examination of persistent swelling in salivary glands [22]. In this study, increased salivary function negatively correlated with disease duration, suggesting that the early diagnosis and treatment of MD are important for the recovery of salivary secretion function.

Küttner tumor is a chronic sclerosing sialadenitis of unilateral or bilateral submandibular gland [23]. Kitagawa et al. described that Küttner tumor showed an increased infiltration of IgG4 plasma cells with marked fibrosis and belongs to the spectrum of IgG4-RD. The complications of Küttner tumor frequently included the other IgG4-RD. Although clinical features of Küttner tumor is similar to that of MD, Küttner tumor showed marked fibrosis in the salivary glands rather than SS [10]. It is thus necessary to elucidate the clinical and histological difference of these diseases, which might eventually lead to distinguish Küttner tumor from other sialadenitis including MD.

Acknowledgements This work was supported by "Research on Measures for Intractable Diseases" Project: matching fund subsidy from the Ministry of Health Labour and Welfare, Japan.

Conflict of interest The authors declare that they have no conflict of interest.

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