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Macrophage Migration Inhibitory Factor (MIF) and Thyroid Hormone Alterations in Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV)

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Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine known to be released from lymphocytes, macrophages and endothelial cells and also in animal models shown to be inducible with glucocorticoids (GC). In contrast, thyroxine seems to antagonize MIF activity. To investigate whether MIF is increased in active antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and possible correlations with GC dosing and thyroid hormone levels, 27 consecutive patients with active AAV were studied and followed prospectively. Disease activity was assessed using Birmingham Vasculitis Activity Score 2003 (BVAS) at baseline and at follow-up at 3 and 6 months, along with MIF, thyroid hormones free triiodothyronine (fT3) and free thyroxine (fT4), C-reactive protein (CRP) and creatinine. MIF was elevated significantly at baseline compared with follow-up at 3 and 6 months (8,618 pg/mL versus 5,696 and 6,212 respectively; $P < 0.002$) but did not correlate to CRP, GC dose, creatinine or organ involvement. fT3 was depressed significantly at baseline compared with follow-up (1.99 pg/mL versus 2.31 and 2.67 respectively; $P = 0.01$) and correlated inversely to the BVAS score at baseline. We found a significant correlation between the MIF/fT4 ratio at baseline versus MIF/fT4 ratio at 6 months ($\rho = 0.52$, $P < 0.005$) and a trend between the baseline MIF/fT3 ratio versus MIF/fT3 ratio at 6 months ($\rho = 0.39$, $P = 0.05$). These results suggest a possible role for MIF and thyroid status in AAV. Further studies could reveal whether the association between AAV and thyroid hormone levels in the context of elevated MIF may present a link as well as a target of treatment.

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INTRODUCTION

Granulomatosis with polyangiitis (GPA, Wegener), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EPGA, Churg-Strauss) are called antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) because of similarities in clinical presentation affecting the small- to medium-sized vessels and their close association with ANCA (1).

The pathogenesis of AAV is not understood fully, although priming of neutrophils by cytokines and the direct action of ANCA on the primed neutrophils are believed to be core elements of the process. The neutrophils then seem to activate complement through the alternate pathway, inducing cytotoxicity, resulting in the necrotizing vasculitis which is the pathological hallmark of the disease which can affect any organ system but commonly involves the joints, the skin, the respiratory tract and the kidneys and, to a lesser extent, the nervous system (2).

Typically, AAV is treated initially with high doses of glucocorticoids (GC) in combination with cyclophosphamide (CYC) (3) methotrexate (MTX) (4) or rituximab (5,6) followed by a maintenance treatment with azathioprine (AZA) and low dose GC (7). The immunosuppressive therapy generally is effective, but frequent relapses, accumulating organ damage and drug toxicity remain a concern. A small subset of patients is also refractory to treatment.

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MIF is a pleiotropic inflammatory mediator released by macrophages, lymphocytes and endothelial cells. MIF is central to the innate immune response system with an upstream role in the inflammatory cascade, promoting the release of other inflammatory cytokines including TNF-α and IL-1β. Furthermore, MIF has a chemokinelike function and promotes recruitment of leukocytes in general and neutrophils specifically into infectious and inflammatory sites (8,9). Previously, MIF has been demonstrated to play a role in sepsis (10,11), autoimmune disease (12–14), chronic kidney disease (15), pulmonary hypertension (16) and cardiovascular disease (17).

Hence, MIF exhibits several specific properties of interest for the onset of AAV. MIF also has been shown to have a reciprocal effect to GC and, in animal models, GC can induce MIF (18). This could, theoretically, counteract the antiinflammatory actions of GC therapy, which is a mainstay of AAV therapy.

The MIF molecule contains a hydrophobic pocket that is important for many of its proinflammatory activities. Several small molecules can inhibit the catalytic activity of this pocket and thereby reduce MIF activity. Thyroxine (T4) has been demonstrated to exhibit such an inhibitory effect on MIF in a dose-dependent manner, whereas the structurally similar triiodothyronine (T3) is, comparatively, only a weak inhibitor of MIF. Furthermore, in a murine sepsis model, thyroxine inhibition of MIF significantly improved survival, suggesting a clinically relevant interaction between T4 and MIF (10). The association between AAV and thyroid disease and the development of ANCA and associated vasculitis with use of antithyroid drugs is long since recognized, making thyroid status of particular interest in these patients (19).

We hypothesized that MIF may play a part in the pathogenesis of AAV and that MIF activity may be related to thyroid hormone levels and corticosteroid dosing in these diseases.

MATERIALS AND METHODS

Patients

Twenty-seven consecutive patients (15 men, 12 women) with active AAV (22 newly diagnosed, 5 relapses) at the Nephrology and Rheumatology Departments at Karolinska University Hospital, Stockholm, Sweden were included in the study and followed prospectively for 6 months. Relapse was defined as an increase in disease activity, reflected by the Birmingham Vasculitis Activity Score 2003 (BVAS), requiring renewed induction treatment.

Seventeen of the patients were diagnosed with GPA, nine patients with MPA and one patient with EPGA according to Chapel Hill 2012 nomenclature (1). Fifteen patients were positive for proteinase 3 (PR-3) ANCA and 12 patients were positive for myeloperoxidase (MPO)-ANCA. Two of the patients had been diagnosed previously with thyroid disease and, subsequently, were treated with thyroid hormone substitution.

Patients received induction treatment for a period of 3 to 6 months; 19 patients received CYC treatment, 4 patients received MTX treatment, 3 patients were treated with rituximab and one patient with mycophenolate mofetil (MMF) as induction therapy, all in combination with GC. Four patients also were treated with plasmapheresis as part of their induction therapy. Three patients were refractory to CYC and were switched to rituximab (patients 3, 25 and 26 in Table 1). Patients in remission were given a maintenance treatment with AZA, MMF or MTX in combination with a low dose of GC.

Methods

Study samples were obtained at baseline and at follow-up at 3 and 6 months. Disease activity was assessed using BVAS (20), chronic damage was assessed using Vasculitis Damage Index (VDI) (21). The dose of GC was calculated in prednisolone equivalent mg and the total amount given up to each timepoint noted along with the prescribed dose on sampling day. Features of the patients including demographics, diagnosis, type of ANCA, organ involvement, CRP, BVAS, creatinine and estimated glomerular filtration rate (eGFR) according to the MDRD equation (22) are shown in Table 1.

Biochemical analysis and ANCA serology by enzyme-linked immunosorbent assay (ELISA) were carried out using routine methods at the Department of Clinical Chemistry and Department of Clinical Immunology at Karolinska University Hospital and included CRP, creatinine, plasma albumin and urine analysis. MIF was analyzed in serum with an ELISA (Young In Frontier Co. Ltd., Seoul, Korea). Plasma MIF levels were compared with results from our previously published control subjects (n = 53) (15). Thyroid hormone function, as assessed by TSH, fT3 and fT4, was analyzed in serum by immunometric assays on an Immulite 1000 Analyzer (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA) according to the instructions of the manufacturers.

The local ethics committee approved the study protocol, and informed consent was obtained from each subject.

Statistics

The patients were examined at 0, 3 and 6 months, and clinical and laboratory data were evaluated for each time point. Unless noted otherwise, normally distributed variables were expressed as means ± standard deviation (SD) and nonnormally distributed variables were expressed as medians and 10 to 90 percentiles. Differences between the timepoints were examined using the Kruskal-Wallis analysis of variance (ANOVA), followed by a *post hoc* Dunn test for nonparametric comparisons. A χ^2 test was used for categorical variables. Correlations (P) were calculated by using the nonparametric Spearman rank test.

Statistical significance was set at the level of $P < 0.05$. All statistical analyses were performed with SAS statistical software (Version 9.2, SAS Institute Inc., Cary, NC, USA).

Table 1. Patient characteristics at baseline.

Patient #	Age	Sex	Diagnosis	ANCA[a]	Organ involvement[b]	CRP[c]	Creatinine/eGFR[d]	BVAS	New/relapse
1	69	M	EPGA	MPO	Pulm, kidneys, skin, joints	61	825/6	27	Relapse
2	60	M	GPA	PR-3	Pulm, kidneys, spleen	51	56/129	25	New
3	27	F	GPA	PR-3	ENT, Pulm, eyes	20	60/104	12	Relapse
4	81	F	MPA	MPO	Pulm, kidneys, Neuro	6	460/Dialysis	34	New
5	74	F	GPA	PR-3	ENT, Pulm	4	73/68	18	New
6	69	M	GPA	PR-3	ENT, Pulm	13	112/56	15	New
7	35	M	GPA	PR-3	ENT	27	74/104	11	New
8	54	M	GPA	PR-3	ENT, joints, kidneys	5	365/11	19	Relapse
9	27	M	GPA	PR-3	ENT, kidneys	1	84/95	16	New
10	67	F	MPA	MPO	Kidneys	1	260/16	12	New
11	54	M	MPA	MPO	Skin, Pulm, kidneys	16	154/41	21	New
12	71	M	GPA	PR-3	ENT, kidneys	33	124/50	9	Relapse
13	61	M	GPA	PR-3	Joints, Pulm, kidneys	6	112/58	19	New
14	65	F	GPA	PR-3	ENT, Pulm, kidneys	40	331/12	30	New
15	72	M	MPA	MPO	Kidneys, Pulm	28	91/71	13	New
16	57	F	MPA	MPO	Kidneys	2	711/5	13	New
17	71	F	MPA	MPO	Kidneys	22	491/8	12	New
18	59	M	GPA	PR-3	ENT, eyes, Pulm	1	65/120	9	New
19	71	F	GPA	MPO	ENT	1	71/70	11	New
20	20	F	GPA	PR-3	ENT, Pulm	33	41/172	10	New
21	35	F	MPA	MPO	Joints, kidneys	1	88/63	8	New
22	59	M	GPA	PR-3	ENT, Neuro, Pulm	2	50/148	10	New
23	81	M	MPA	MPO	Kidneys, Pulm	82	170/34	18	New
24	59	M	GPA	PR-3	ENT, joints, Pulm	3	74/94	7	New
25	71	M	GPA	PR-3	ENT, joints, Pulm, skin, kidneys	14	69/98	17	New
26	64	F	GPA	MPO	Joints, Pulm, kidneys	8	141/33	18	New
27	19	F	MPA	MPO	Kidneys	1	83/77	5	Relapse

Abbreviations: M, Male; F, Female; ENT, ear, nose, and throat; Pulm, pulmonary system; Neuro, neurological system.
[a]ANCA antibodies were directed against MPO or PR-3.
[b]Joints refers to arthralgia or arthritis in the joints.
[c]CRP reference was <1 mg/L.
[d]Creatinine reference was <100 μmol/L for males and <90 μmol/L for females; eGFR is calculated using the MDRD formula.

RESULTS

Disease activity measured as BVAS dropped from a mean of 15.4 at baseline to 1.9 at 3 months and 1.0 at 6 months ($P < 0.001$) whereas disease-associated chronic damage measured as VDI increased from 0.64 at baseline to 1.46 at 3 months and 1.64 at 6 months ($P = 0.002$). There was no mortality in the study.

MIF was elevated at significantly baseline compared with follow-up at 3 and 6 months: 8,618 pg/mL versus 5,696 pg/mL and 6,212 pg/mL respectively ($P < 0.001$) (Figure 1). The mean total steroid dose in prednisolone equivalent milligrams was: 1,150 mg (range 0–3,125 mg) at baseline, 4,172 mg (range 1,705–5,582 mg) at 3 months and 5,531 mg (range 2,625–7,467 mg) at 6 months. The mean dose at sampling day was: 137.5 mg (range 0–625 mg) at baseline, 21.5 mg (range 10–50 mg) at 3 months and 14 mg (range 5–50 mg) at 6 months.

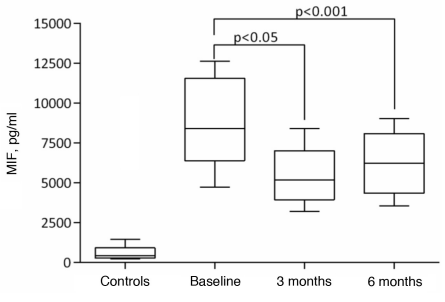

Figure 1. Levels of macrophage migration inhibitory factor (MIF) of controls and patients at baseline and at follow-up.

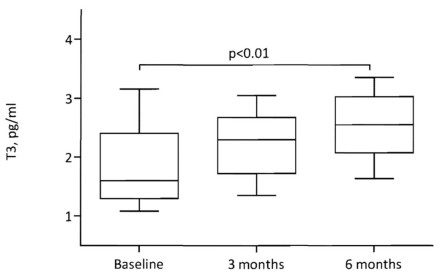

Figure 2. Levels of free triiodothyronine (fT3) at baseline and at follow-up.

Table 2. Biochemical and clinical parameters at baseline, 3 and 6 months.[a]

	Baseline	3 months	6 months	*P* value
BVAS	15.4	1.9	1.0	<0.001
VDI	0.64	1.66	1.75	0.002
MIF (pg/mL)	8,618	5,996[b]	6,212[c]	<0.002
TSH (uIU/mL)	1.20	1.49	1.71	NS
fT3 (pg/mL)	1.99	2.31	2.66[c]	<0.01
fT4 (ng/dL)	1.35	1.19	1.23	NS
CRP (mg/L)	17.9	4.4	6.2	NS
Creatinine (μmol/L)	194	162	157	NS
Albumin (g/L)	31.8	35.2[b]	35.8[c]	0.01
GC (mg, mean dose)	137.5	21.5[b]	14[c]	0.001
Hematuria >10 RBC/HPF (%)	48	16[b]	16[c]	0.002

[a]TSH reference was 0.4–4 uIU/mL; fT3 reference was 1.5–4.1 pg/mL; fT4 reference was 0.89–1.76 ng/dL, Albumin reference was 34–45 g/L. Dose of GC is in prednisolone equivalent milligrams.
[b]Comparison between baseline and 3 months.
[c]Comparison between baseline and 6 months.

fT3 was depressed significantly at baseline compared with follow-up: 1.991 pg/mL versus 2.313 and 2.665 respectively ($P < 0.01$) (Figure 2) whereas there were no significant changes in fT4, TSH, creatinine and CRP during the course of the study (Table 2). The percentage of patients with hematuria was significantly different at onset and follow-up; 48% versus 16% ($P = 0.002$) while plasma albumin increased significantly ($P = 0.01$). Omitting the two patients with thyroid hormone substitution did not change our findings.

Univariate and Multivariate Correlates

There was no significant correlation between MIF levels and kidney, lung or any other organ manifestation, nor did MIF correlate to CRP or creatinine at any timepoint. There was no correlation between MIF levels and GC exposure or dose at sampling day at baseline, 3 or 6 months. There was a trend toward an inverse correlation between fT3 and MIF levels, although it did not reach significance ($\rho = -0.25$; $P = 0.30$). However, we found a significant correlation between the ratio of MIF/fT4 at baseline versus the MIF/fT4 ratio at 6 months ($\rho = 0.52$, $P < 0.005$) as shown in Figure 3B. There was a correlation trend between the ratio of baseline MIF/fT3 versus MIF/fT3 ratio at 6 months ($\rho = 0.39$, $P = 0.05$) as shown in Figure 3A. fT3 correlated inversely to BVAS ($\rho = -0.47$, $P = 0.02$), Figure 3C, and to creatinine at all timepoints (data not shown).

DISCUSSION

In our study, we found that MIF was increased markedly in active AAV compared with remission. This was independent of creatinine, CRP, organ involvement and exposure to GC. These findings are in line with the role of MIF as a proinflammatory mediator from previous studies in other autoimmune disorders (12–14) and in sepsis (10,11).

Previous investigators have reported increased MIF levels in AAV compared with controls as well as in patients with other types of granulomatous disease (23,24). A small number of patients also have been studied longitudinally, however a consistent follow-up and record of organ manifestations was essentially lacking in these studies (23).

It is not surprising to find MIF implicated in many different inflammatory conditions since it seems to have an upstream role in the inflammatory cascade by promoting the release of other inflammatory cytokines. This is demonstrated by the observation that genetic deletion of MIF results in a global decrease of macrophage mediators including TNF-α, IL-1β, IL-12 and PGE2 (25).

An important mechanism for resolving inflammation is the timely removal

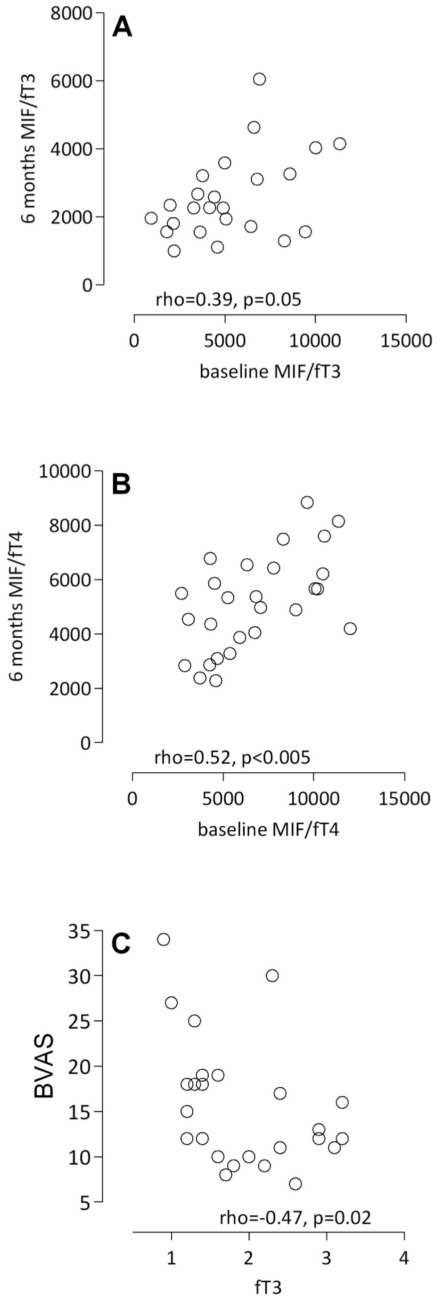

Figure 3. Correlation between MIF/fT3 at baseline and 6 months. (B) Correlation between MIF/fT4 at baseline and 6 months. (C) Correlation between fT3 levels and BVAS.

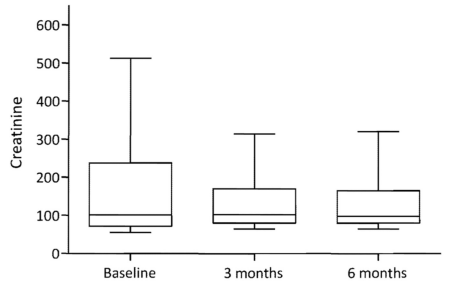

Figure 4. Levels of creatinine at baseline and at follow-up.

of activated monocytes/macrophages by apoptosis. In the presence of high concentrations of MIF, this is suppressed by inhibiting p-53 dependent apoptosis, giving rise to an extended immune response with TNF-α and IL-1β production, leading to further MIF release (26). In the pathogenesis of AAV, priming of neutrophils by cytokines is a key feature (2), and high levels of MIF could contribute to this (8,11).

MIF and GC seems to have reciprocal effects on the immune system and, unlike other cytokines, low doses of GC seem to be able to induce MIF, at least in animal models (18). This finding has led to an interest in anti-MIF treatment as a GC-sparing treatment in autoimmune conditions and, already, there are agents available, both small molecules and antibodies with an inhibitory effect on MIF (26). However, in our study, we could not find any correlation with GC dose and MIF levels, possibly due to the timing of sampling or the high, unphysiological doses given. Nevertheless anti-MIF treatment may have a therapeutic potential in AAV. Tam *et al*., who assessed the effect of anti-MIF antibodies on rats with established experimental glomerulonephritis, provide an early indication of this. Proteinuria, glomerular macrophage infiltration and glomerular crescents were reduced in a dose-dependent manner in anti-MIF antibody-treated rats compared with controls. In addition, urinary levels of proinflammatory cytokines including TNF-α and IL-1β were reduced, leading the authors to conclude that anti-MIF antibodies have important clinical potential in nephritis and other MIF-related diseases (27).

Although AAV is rarely seen concurrently with other autoimmune diseases, a clear association between AAV and thyroid disease exists (19). Furthermore, treatment with antithyroid drugs is associated with the development of ANCA and associated vasculitis (28). Even though this association is well known, to our knowledge, thyroid hormone status has not been reported in incident AAV patients. Recently thyroxine has been proven to be a potential endogenous inhibitor of MIF, offering a potential link between AAV and thyroid disease (10).

The most striking abnormality in thyroid hormone levels seen in our study is low fT3 in active disease compared with remission with a baseline fT3 correlation to disease severity measured as BVAS. This resembles the "euthyroid sick syndrome" described in other severely ill patients (29), most notably sepsis, where low T3 and T4 concentrations are associated with more severe disease and worse outcome. In autoimmune conditions, subclinical hypothyroidism is well described in systemic lupus, particularly lupus nephritis (30). These thyroid hormone disturbances in sick patients may be explained with renal impairment, stress responses, impaired tissue function, altered peripheral thyroid hormone metabolism and medication, among others (31). Still the pathogenesis remains poorly understood.

We found a significant correlation between the ratio of MIF/fT4 at baseline versus MIF/fT4 ratio at 6 months and a correlation trend between the ratio of baseline MIF/fT3 versus MIF/fT3 ratio at 6 months consistent with the notion that there may be an interaction between these molecules in AAV as described earlier in sepsis (10).

Although MIF and thyroid hormones each on their own have been studied in other autoimmune diseases, the potential interaction between these molecules has not been addressed previously. Whether this interaction is of clinical importance should be explored in further studies.

There was a correlation between fT3 and creatinine at all timepoints. However, these results may be difficult to interpret as creatinine itself did not change significantly throughout the study (Figure 4).

CONCLUSION

Our study demonstrated increased circulating MIF levels and alterations in thyroid hormone levels in active AAV compared with remission, but did not support a clinically relevant induction of MIF by GC therapy at the high doses given routinely in AAV. Thyroxine has been identified previously as a potential endogenous inhibitor of MIF, and our findings appear to indicate that an MIF-thyroxine interaction may be important in AAV as well (10). Further studies could reveal whether the association between AAV and thyroid levels in the context of elevated MIF may present a link as well as a target of treatment.

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DISCLOSURE

The authors declare that they have no competing interest as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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