Antibodies Against Serotonin Have No Diagnostic Relevance in Patients with Fibromyalgia Syndrome

EGON WERLE, HEINRICH P. FISCHER, ANNETTE MÜLLER, WALTER FIEHN, and WOLFGANG EICH

ABSTRACT. ***Objective.*** To determine the prevalence and potential diagnostic relevance of autoantibodies against serotonin, thromboplastin, and ganglioside Gm1 in patients with fibromyalgia syndrome (FM).
Methods. Sera from 203 patients with FM and 64 pain-free control subjects were analyzed with enzyme immunoassays. Clinical and psychometric data of the patients were analyzed for the presence or absence of autoantibodies.
Results. Compared with control subjects patients with FM had a significantly higher prevalence of autoantibodies against serotonin (20% vs 5%; $p = 0.003$) and thromboplastin (43% vs 9%; $p < 0.001$), but not against ganglioside Gm1 (15% vs 9%; $p = 0.301$). Differences in autoantibody prevalence between controls and FM patients were not related to age or sex. No association was found between autoantibody pattern and clinical or psychometric data, e.g., pain, depression, pain related anxiety, and activities of daily living.
Conclusion. There is an elevated prevalence of antibodies against serotonin and thromboplastin in patients with FM. The pathophysiological significance of this finding is unknown. Calculation of positive predictive values of antiserotonin antibodies shows that measurement of these antibodies has no diagnostic relevance. (J Rheumatol 2001;28:595–600)

Key Indexing Terms:
FIBROMYALGIA SEROTONIN AUTOANTIBODIES
THROMBOPLASTIN GANGLIOSIDE Gm1

Fibromyalgia syndrome (FM) is a noninflammatory disease with chronic widespread pain and a lowered pain threshold of muscles, tendons, and skin for mechanical, thermal, electrical, and chemical stimulants[1-5]. Patients with FM typically have a large number of nonspecific symptoms, e.g., fatigue, sleeping disorders, irritable bowel syndrome, depression[2]. FM is a common disease with a prevalence of 1.9–3.4% in Germany and the USA[6,7] and has an enormous social and financial impact[8]. The diagnosis is based purely on clinical findings and history[9]; no laboratory test for FM is available.

The etiology of FM remains elusive. Primary muscle abnormalities, either structural or functional, can explain neither muscle tenderness[10] nor tenderness of other tissues. Current concepts of the pathophysiology of FM focus on the neuroendocrine and the central nervous system. Several neurohormonal perturbations have been described in FM, e.g., low integrated basal cortisol levels, exaggerated adrenocorticotropic hormone response after exogenous application of corticotropin releasing hormone, low plasma levels of neuropeptide Y, and elevated cerebrospinal fluid levels of substance P[11-14]. Moldofsky[15] proposed that a deficiency of serotonin might be a pathogenetic factor in FM, and indeed, serotoninergic activity was found to be lowered[12]. The levels of serotonin (5-hydroxy-tryptamine, 5HT) and/or its metabolites have been reported to be lower than normal in serum[16], cerebrospinal fluid[17], and circulating platelets in FM[18]. A review of these data and a discussion of the possible mechanisms have been published[13]. In 1992, Klein, *et al* reported a high prevalence of antibodies against serotonin and gangliosides in patients with FM compared to healthy controls[19]. The pathophysiological rationale for measuring antibodies against gangliosides that have been shown to be part of the serotonin receptor[20] was their possible effect on serotonin receptor function. Klein and Berg raised the intriguing hypothesis that FM may be a "psycho-neuro-endocrinological autoimmune disease" with a typical autoantibody pattern[21,22].

We analyzed antiserotonin antibodies in relation to clinical and psychological data in a large, well defined cohort of FM patients participating in a multicenter intervention study[23]. In addition, the diagnostic power of testing antiserotonin antibodies in patients with FM was evaluated.

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MATERIALS AND METHODS

Subjects. A total of 203 consecutive patients [92% female, age 52 (mean) ± 6.9 (SD) yrs] who fulfilled the criteria of the American College of Rheumatology[9] for FM were recruited in one outpatient (n = 35) and 5 inpatient rheumatology clinics (n = 168) in southwest Germany.

Exclusion criteria were significant comorbidity with other rheumatic or psychiatric diseases, age over 65 years, and insufficient language skills. All these patients took part in a multicenter therapy study[23]. Clinical and psychological testing was done and blood samples were obtained before treatment. Patients did not take part in other clinical trials before they entered the study.

Sixty-four pain-free control subjects [55% female, patients from the Department of Internal Medicine (n = 19) and clinical staff (n = 45), mean age 37 ± 20.7 (SD) yrs] were enrolled. The pain-free patients were recruited consecutively after admission to the Department of Internal Medicine II (cardiology and gastroenterology) in Heidelberg. Clinical staff were recruited consecutively at their yearly health checkup. Exclusion criteria for both groups were pain and significant comorbidity with rheumatic or psychiatric diseases.

Psychological assessment. Pain intensity was recorded with a visual analog scale (VAS; scale of 0 to 10 cm). Depression was assessed with the short form (15 items; scale of 0 to 45) of the ADS questionnaire[24], which is a validated German version of the Center for Epidemiologic Studies Depression Scale[25]. The scale for pain related anxiety is part of a validated German questionnaire for coping strategies in patients with chronic pain (FESV[26]) and has a range from 4 to 24. Functional capacity was assessed with a validated German questionnaire for patients with musculoskeletal pain, the Hannover Functional Status Questionnaire (FFbH[27]), which has a range 0–100%. The FFbH is an 18 item questionnaire measuring limitations in activities of daily living. It is comparable to the Health Assessment Questionnaire (HAQ) and the 2 scales are highly correlated (r = 0.87)[28].

Materials and laboratory methods. Antibodies against serotonin, gangliosides, and phospholipids were determined by ELISA as described[19,21]. Antigens for coating microtiter plates were gangliosides (monosialoganglioside Gm1 from bovine brain; G-7641, Sigma, Deisenhofen, Germany) and serotonin (5HT; H8502, Sigma). The purity of serotonin was verified by high performance liquid chromatography. Antithromboplastin antibodies were detected with a mixture of phospholipids and protein as the coating material (Sigma). Microtiter plates (Immunoplate II-Maxisorp microplates) were from Nunc (Roskilde, Denmark).

Serum dilutions of 1:500 were used for detection of antiserotonin and antiganglioside antibodies and a dilution of 1:1000 for measurement of antithromboplastin antibodies.

Antigen concentration for coating of microtiter plates with 10 µg/l for each antigen was achieved by dilution in hydrogen carbonate buffer, 0.2 M, pH 9.6, and 100 µl were incubated in microtiter plates overnight at 4°C. After 3 washing steps with phosphate buffered saline (PBS), pH 7.4, containing 1% bovine serum albumin (BSA V, order number 735094; Boehringer Mannheim, Mannheim, Germany), the plates were incubated with this buffer for 1 h at room temperature to block free binding sites. Then the buffer was discarded and 100 µl of the diluted patient and control sera were incubated 1.5 h. After washing with PBS containing 0.5% BSA and 0.1% Triton X-100 (Serva, number 37238), peroxidase conjugated immunoaffinity purified $F(ab)_2$ fragment goat anti-human IgG (for Gm1 and serotonin: Fcγ fragment-specific, code number 109-036-098; for thromboplastin: goat anti-human IgG, code number 109-035-003) and immunoaffinity purified goat anti-human IgM (for Gm1, serotonin, and thromboplastin: $Fc_{5\mu}$ fragment-specific, code number 109-035-043) antibodies (Dianova, Hamburg, Germany) were added in parallel at a dilution of 1:3000. The plates were incubated 1 h at room temperature and then washed 3 times. Bound horseradish peroxidase activity was then determined using 150 µl o-phenylenediamine (OPD; Sigma number P-4664) as chromogen (0.5 mg OPD/ml in 0.2 M citrate buffer, pH 5.0, and 0.01% H_2O_2). Color development was stopped by addition of 50 µl sulfuric acid and the absorbance was measured in an ELISA reader (Dynatech MR7000; Las Vegas, Nevada, USA). Nonspecific binding determined by incubating patient and control sera also with uncoated plates was taken into account when calculating specific binding data.

Three sera with high, medium, and low antibody levels against serotonin as well as a negative control were used as standard sera. The highest optical density values were 1.4 and 1.2 for antiserotonin antibodies of the IgM and IgG class, respectively. These sera were kind gifts from R. Klein (Department of Internal Medicine II, Medical Clinic and Policlinic, University of Tübingen).

Statistical analysis. Antibody concentrations were dichotomously categorized as normal or elevated based on the 95th percentile of the optical density values of the ELISA measurements of sera from the control subjects. Antibodies were considered positive when elevated autoantibody concentrations of the IgG or IgM class or both immunoglobulin classes were found. The 95% confidence interval (95% CI) is given for the most important prevalence data. The positive predictive value (PPV) was calculated according to the following algorithm: number of FM patients with pathological concentrations divided by the number of all subjects with pathological concentrations. If not stated otherwise, data are given as mean ± standard deviation (SD). Median, 25th and 75th percentiles, and 5th and 95th percentiles for questionnaire data are illustrated. Prevalence of antibodies in patients and controls was compared by Fisher's exact probability test. In FM patients, association between age and antibodies was assessed by 3 different approaches: Student's t test, Mantel-Haenszel chi-square, and Fisher's exact probability test. First, age of negative and positive individuals was compared by an independent samples T test. Second, patients were divided in quintiles according to age. Association between age and antibodies was tested by Mantel-Haenszel chi-square. Third, the first and the last quintile were compared with respect to the prevalence of antibodies by Fisher's exact probability test.

Questionnaire data of FM patients with and without antibodies were compared by the Mann-Whitney U test. A 2 tailed p value ≤ 0.05 (alpha = 5%) was considered statistically significant. Bonferroni correction was performed to maintain the error level of alpha. The software package SAS for Windows 6.11 was used (SAS Institute, Cary, NC, USA).

Enrolling 203 patients with FM and 64 controls and assuming a prevalence of antiserotonin antibodies of 5% or less in controls[19,21], we had at least a 95% chance of detecting a difference of 15% between controls and FM patients with a one-sided alpha level of 5%[29].

RESULTS

Prevalence of autoantibodies against serotonin, thromboplastin, and ganglioside Gm1 is illustrated in Figure 1, which also shows whether autoantibodies of the IgG class or IgM class or both were detected. In patients with FM the prevalence of IgG and/or IgM antibodies against serotonin was significantly higher than in controls [20% (95% CI 15%–26%) vs 5% (95% CI 2%–13%); p = 0.003]. In addition, antibodies against thromboplastin were more frequent in FM patients than in controls [43% (95% CI 36%–50%) vs 9% (95% CI 4%–19%); p < 0.001]. In contrast, the prevalence of antibodies against the ganglioside Gm1 was similar in patients and controls [15% (95% CI 11%–21%) vs 9% (95% CI 4%–19%); p = 0.301].

The prevalence of the autoantibodies under investigation was not age related. FM patients without or with autoantibodies against serotonin, thromboplastin, or ganglioside Gm1 were of similar age (52 ± 7 vs 52 ± 8; 52 ± 7 vs 52 ± 7; 52 ± 7 vs 51 ± 7 yrs, respectively) and duration of disease

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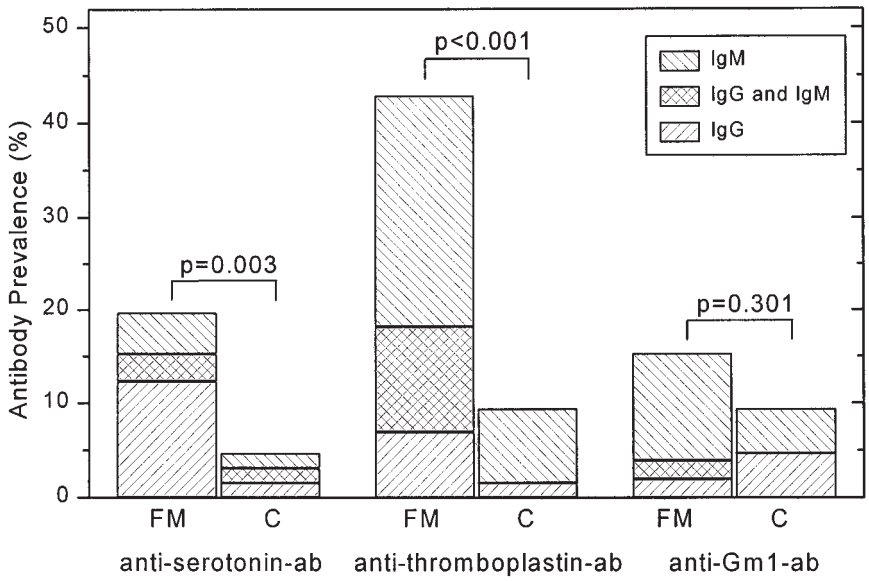

Figure 1. Prevalence of antiserotonin, antithromboplastin, and antiganglioside Gm1 antibodies was determined in 203 patients with FM and in 64 pain-free controls (C) by ELISA. Stacked columns represent prevalence of IgG or IgM class antibodies and of both IgG and IgM antibodies.

was comparable (7.5 ± 7.0 vs 7.9 ± 8.3; 7.7 ± 8.1 vs 8.7 ± 10.8; 7.4 ± 6.6 vs 8.3 ± 6.0 yrs, respectively).

Analyzing subgroups of patients without and with the 3 autoantibodies we found no differences in any of the relevant clinical variables, e.g., pain, depression, anxiety, functional capacity (Figures 2–4).

The sensitivity of 20% and the specificity of 95% together with the disease prevalence contribute to the PPV of antiserotonin antibodies for the diagnosis of FM. With a prevalence of about 5%, as reported for women at an age of about 50 years[7], the PPV is 0.17. This means that only about one of 5 positive test results is really from a patient with FM, and vice versa, 4 out of 5 positive results were received from non-FM subjects. At a given prevalence of 30%, which might occur only in very specialized outpatient clinics, the probability to obtain a positive test result from FM patients would still only be about 50%.

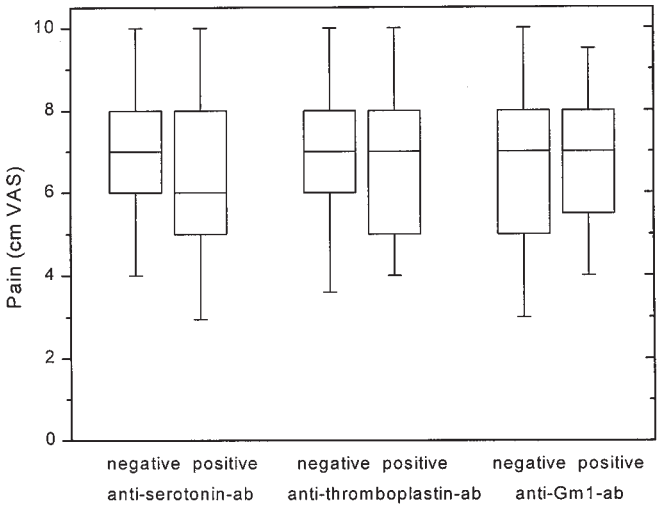

Figure 2. Pain intensity of patients with FM (n = 203) in relation to the absence (negative) or presence (positive) of antibodies against serotonin (n = 162 vs n = 41, respectively), thromboplastin (n = 116 vs n = 87), and ganglioside Gm1 (n = 173 vs n = 30).

DISCUSSION

Fibromyalgia syndrome is one of the most frequent rheumatic disorders and shows a wide spectrum of different symptoms. The etiology and pathophysiology of FM is controversial[10,30-33]. In 1992 Klein, *et al* were the first to describe an elevated prevalence of antibodies against serotonin and gangliosides in patients with FM compared to healthy controls[19]. In 1995 they reported that 49% of FM patients had antiserotonin, antiganglioside, and antithromboplastin antibodies in parallel and 70% of patients had at least 2 of these antibodies[22].

In 2 reports of quite small groups of FM patients, elevated antiserotonin and antiganglioside autoantibody prevalence could not be confirmed[34,35]. We measured these autoantibodies in a large cohort of patients with well defined FM to contribute to clarification of these conflicting data. For this purpose we were in close contact with the authors of the original investigation and reproduced their technique in detail[19].

In this study antiganglioside antibody frequency was not increased in patients with FM compared to pain-free subjects. We could detect neither the high prevalence of more than 70%[19,21] nor a lower frequency in comparison to

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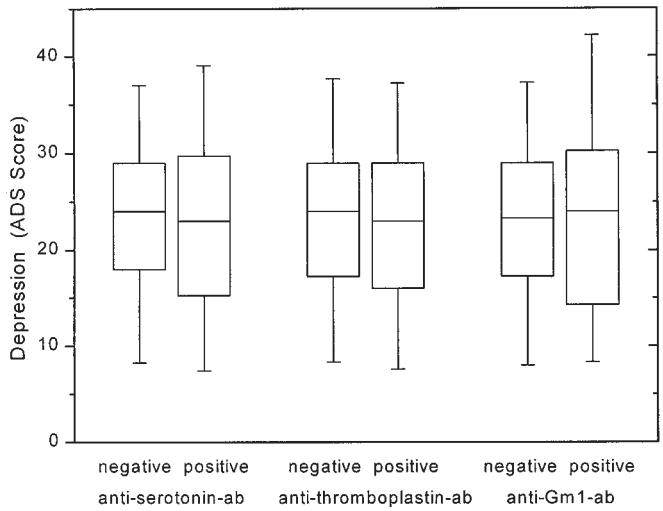

Figure 3. Depression (ADS) score[24] in patients with FM (n = 203) in relation to the absence (negative) or presence (positive) of antibodies against serotonin, thromboplastin, and ganglioside Gm1.

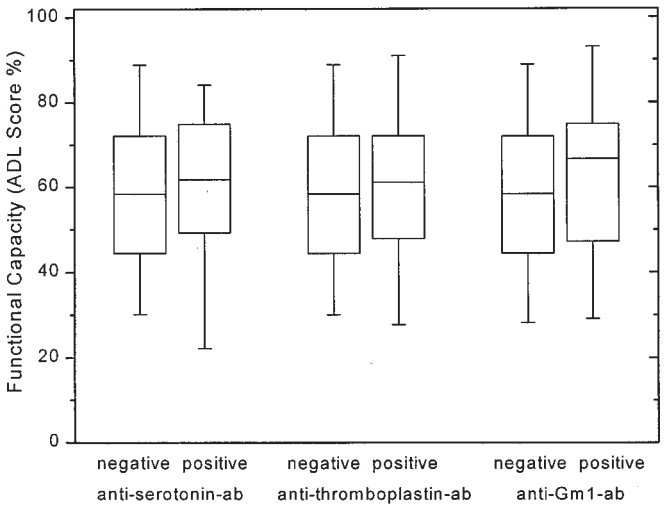

Figure 4. Activities of daily living (ADL) score in patients with FM (n = 203) in relation to the absence (negative) or presence (positive) of antibodies against serotonin, thromboplastin, and ganglioside Gm1.

controls[34]. Thus we cannot substantiate the hypothesis that autoantibodies against gangliosides, which are part of the serotonin receptor[20], may affect serotoninergic neurotransmission in FM and thereby contribute to FM symptomatology.

The prevalence of antithromboplastin antibodies in our study (43%, 95% CI 36%–50%), however, is in quite good agreement with the data of Klein and colleagues (54%, 95% CI 44%–63%)[22]. The pathophysiological significance of these autoantibodies is unclear. The rate of thrombosis is not increased in patients with FM and elevated levels of antiphospholipid antibodies have not been investigated so far.

The antiserotonin antibody may be the most interesting one. Recently, elevated plasma antiserotonin antibodies were found in patients with panic disorder[36]. It had been suggested that these antibodies are quite specific for FM[22], and one may speculate on their involvement in the pathophysiology of FM. However, elevated prevalence of antiserotonin antibodies in the first report (74%; 95% CI 60%–84%; n = 50)[19] and a later publication (73%; 95% CI 64%–81%; n = 100)[21] could not be confirmed by others[34,35]. In our study the prevalence of antibodies against serotonin in patients with FM was significantly higher than in pain-free controls (20% vs 5%). Bearing in mind that autoantibodies are more frequent in elder subjects, we statistically analyzed the age dependency of autoantibody patterns. However, age and sex did not influence the prevalence of any of the autoantibodies investigated and could not explain the differences between patients and controls. Moreover, the specificity of the antiserotonin autoantibody measurements in our study (95%, n = 203) and in the previous report[19] was nearly identical (94%; n = 32).

In addition, we performed post hoc power analyses with the data of researchers who failed to detect significantly different antiserotonin antibody levels between controls and patients with FM[34,35]. The investigations of Welin, *et al*[35] (30 FM patients, 30 controls) and Russell, *et al*[34] (44 FM patients, 48 controls) had enough power (> 0.9) to detect the difference reported by Klein, *et al*[19]; however, these studies had not sufficient power to detect the differences between FM patients and controls that we describe. Therefore, we conclude that the prevalence of antiserotonin antibodies is indeed elevated, as suggested by Klein, *et al*[19], but not as high as initially assumed. Our conclusion is in good agreement with other results: Günaydin and colleagues reported elevated antiserotonin antibody levels in 31.7% of 104 patients with FM (95% CI 24%–41%)[37]. The 95% confidence intervals of our and Günaydin's antiserotonin antibody prevalence overlap, which indicates no statistical difference in the prevalence of this autoantibody in the 2 studies.

Besides determination of the prevalence of autoantibodies in FM we also evaluated the association of autoantibody patterns with clinical and psychometric data, which has not been done previously. However, there was no correlation of antibody levels with any of the relevant clinical variables in FM, e.g., pain, depression, pain related anxiety, and activities of daily living. The presence of antibodies was not confined to a special subgroup of FM patients, and finally, there was no obvious explanation for the higher prevalence of antiserotonin antibodies or antithromboplastin antibodies in FM patients.

In principle, elevation of serotonin and antithromboplastin antibodies could be drug induced. For instance, selective serotonin reuptake inhibitors (SSRI) react with the serotonin reuptake receptor and therefore presumably have

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a complementary structure. Antibodies against SSRI might therefore be antiidiotypes of serotonin antibodies. Given a sufficiently high degree of similarity, antiidiotypic antibodies could react with the related epitope and bind to the serotonin receptor[36,38]. However, at the time of this study SSRI were a rare medication for treatment of FM in Germany. Only 4 (2%) of our patients took SSRI (all of them fluoxetine). None of these patients was positive for any of the 3 tested antibodies. In addition, we did not find a significant difference in antibody levels between patients who took amitriptyline and those who did not (data not shown).

We describe a quite low sensitivity of 20% of antibodies against serotonin in patients with FM, and for decision making one has to bear in mind the positive predictive value of a test result that depends largely on the prevalence of the disease in the patient group tested. However, the question of why there are significant differences in autoantibody patterns between patients with FM and healthy controls requires further research.

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