Possible Association Between Anti-Trisulfated-Heparin-Disaccharide Immunoglobulin M Autoantibody and Fibromyalgia Syndrome

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ABSTRACT **Background:** Fibromyalgia syndrome (FMS) is estimated to affect 2–4% of the general population. While FMS has some known environmental and genetic risk factors, the disorder has no clear etiology. A common coexisting disorder with FMS is small fiber neuropathy (SFN). High levels of serum Immunoglobulin M (IgM) binding to trisulfated-heparin-disaccharide (TS-HDS) were recently found to be associated with SFN.

Objectives: To evaluate potential differences in anti-TS-HDS antibody titers in women with FMS compared to healthy controls.

Methods: In this cross-sectional study, we evaluated 51 female participants: 30 with a diagnosis of FMS and 21 healthy controls who had been recruited at the Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Israel. All of the participants were older than 18 years of age. Anti-TS-HDS IgM levels were measured in their sera using the enzyme immunoassay technique.

Results: The mean anti-TS-HDS IgM levels were significantly lower in the FMS group, compared with the control group (7.7 ± 5 vs. 13.2 ± 8.6 U/ml, respectively; $P = 0.013$).

Conclusions: There is a possible association between FMS and anti-TS-HDS IgM. This association might be the missing link for the coexistence of SFN and FMS, but further study should be performed to assess this association and this auto-antibody characteristic.

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KEY WORDS: autoantibodies, autoimmune disease, fibromyalgia, neuropathic pain, small fiber neuropathy

Fibromyalgia syndrome (FMS) is a common disorder affecting 2–4% of the general population [1]. The main clinical manifestation of FMS includes widespread chronic pain, which is frequently accompanied by sleep disorders, fatigue, and memory problems [2,3]. The diagnosis of FMS is based on clinical features. Currently, there are no measurable diagnostic tools for this disorder [3,4]. While there is no clear etiology of FMS, some environmental and genetic risk factors have been described [4]. Several hypotheses regarding the pathogenesis of FMS have raised possible pathogenic pathways, such as central sensitization [5,6] and dysautonomia-related neuropathic pain as facilitators of FMS [7].

Small fiber neuropathy (SFN) is a common co-morbidity of FMS, which coexists in up to 40% of FMS patients. SFN is a disorder of the peripheral nerves, mainly affecting small autonomic and somatic fibers [8]. Both disorders share several symptoms, including chronic pain and paresthesia, and similar genetic associations such as variants of the SCN9A gene, which encodes the dorsal root ganglia sodium channel Nav1.7 [4,7,9,10]. The association between high levels of serum Immunoglobulin M (IgM) binding to trisulfated-heparin-disaccharide (TS-HDS) and SFN was recently observed, mainly in relation to non-length-dependent SFN (NLD-SFN) among women [11,12].

We assessed the potential changes in the titter of anti-TS-HDS IgM between women with FMS and healthy controls to evaluate a potential association between this unique autoantibody and FMS.

PATIENTS AND METHODS

PATIENT RECRUITMENT

Fifty-one female participants were enrolled in this cross-sectional study; 30 with a diagnosis of FMS and 21 healthy controls. All of the participants were recruited at the Zabludowicz Center for Autoimmune Diseases in Sheba Medical Center, Is-

rael. The data were collected and evaluated in 2021. All patients and healthy controls enrolled in the study were women older than 18 years of age.

FMS DIAGNOSIS

The diagnosis of FMS was made by physicians in our center, based on the ACR 2016 criteria [13]. Peripheral blood samples were collected from the participants on recruitment.

QUANTIFICATION OF CIRCULATING LEVEL OF ANTI-TS-HDS IGM ANTIBODY

Anti-TS-HDS IgM levels were evaluated by enzyme immunoassay (EIA) at CellTrend GmbH laboratory (Luckenwalde, Germany).

ETHICS APPROVAL

This study was confirmed by the institutional review board of Sheba Medical Center, Tel Hashomer, Israel, and conducted according to the Declaration of Helsinki.

STATISTICAL ANALYSIS

Categorical variables were presented as percentages and continuous variables as means ± standard deviations. The comparison between the groups was made by student T-test or its non-parametric versions for continuous variables and the chi-square test or Fisher's test for categorial variables. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA). Data visualization was performed using Plotly 15.3.0 library. $P < 0.05$ was considered statistically significant.

RESULTS

The mean age of patients in the FMS group was significantly higher than the control group (51.5 ± 14.9 years vs. 34.9 ± 10.3 years, respectively; $P < 0.001$). There were no statistically significant differences in the academic education or socioeconomical strata between the groups, and neither had differences in their smoking habits [Table 1].

The majority of the patients with FMS had widespread pain (96.7%), arthralgia (96.7%), myalgia (96.7%), fatigue (93.3%), sleep disorder (90%), memory impairment (83.3%), paresthesia (83.3%), vertigo (73.3%), headaches (66.7%), and vision abnormalities (66.7%). All of these symptoms were relatively rare in the control group (except for headache in 28.6% and vision abnormalities in 14.3%. All the other symptoms < 10%) [Table 2].

Notably, the mean anti-TS-HDS IgM levels were significantly lower in the sera of the FMS group, 7.7 ± 5 U/ml, compared with 13.2 ± 8.6 U/ml in the control group ($P = 0.013$) [Table 1, Figure 1]. Among patients with FMS, none of the symptoms was found to be associated with anti-TS-HDS IgM levels (nor in the control group).

Table 1. Patient baseline characteristics

	Total (n=51)	Fibromyalgia group (n=30)	Controls (n=21)	*P* value
Female	51 (100%)	30 (100%)	21 (100%)	
Age in years	45.5 ± 15.5	51.5 ± 14.9	34.9 ± 10.3	< 0.001
Academic education	31)60.8%)	15 (50%)	16 (76.2%)	0.059
High SES	26 (51%)	17 (56.6%)	9 (42.9%)	0.236
Smoking	8 (15.7%)	6 (20%)	2 (9.5%)	0.321
TS-HDS IgM levels (U/ml)	10 ± 7.2	7.7 ± 5	13.2 ± 8.6	0.013

Continuous variables are presented as mean ± standard deviation
IgM = immunoglobulin M, SES = socioeconomic status, TS-HDS = trisulfated-heparin-disaccharide (TS-HDS)

Table 2. Patient symptoms

	Controls (n=21)	Fibromyalgia group (n=30)
Fatigue	2 (9.5%)	28 (93.3%)
Widespread pain	0 (0%)	29 (96.7%)
Sleep disturbances	1 (4.8%)	27 (90%)
Memory impairment	2 (9.5%)	25 (83.3%)
Vision abnormalities	3 (14.3%)	20 (66.7%)
Headache	6 (28.6%)	20 (66.7%)
Vertigo	1 (4.8%)	22 (73.3%)
Arthralgia	0 (0%)	29 (96.7%)
Myalgia	2 (9.5%)	29 (96.7%)
Paresthesia	2 (9.5%)	25 (83.3%)

DISCUSSION

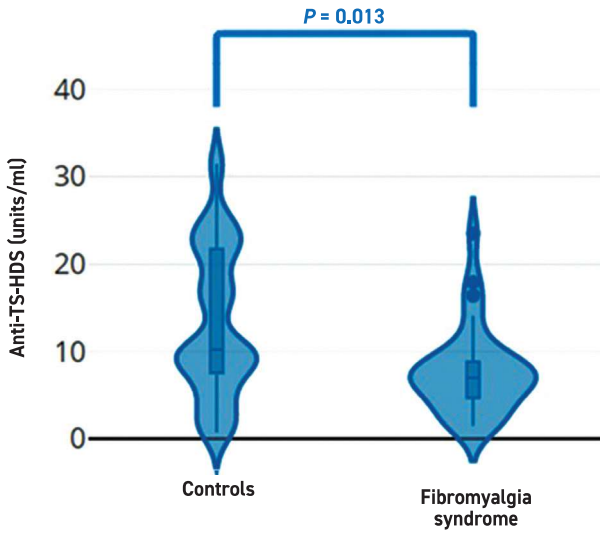
There is no specific biomarker or immune parameter that is linked with FMS or its clinical features [3,4]. We found a possible association between FMS and anti-TS-HDS IgM levels.

The ACR diagnostic criteria for FMS are based on the assessment of the patient's symptoms, including widespread pain, fatigue, unrefreshed waking, and cognitive symptoms [3]. The lack of an objective tool supporting the diagnosis make the diagnosis and management of patients with FMS challenging. Several reports showed that the diagnosis of FMS was described as a lengthy process that required 3.7 encounters with different physicians and took more than 5 years before the final diagnosis was determined [14,15]. The absence of an objective marker emphasizes the importance of finding a possible quantitative tool for physicians to diagnose and assess FMS patients.

Figure 1. A significant reduction of anti-TS-HDS IgM titter in women with fibromyalgia syndrome vs. healthy women

Anti-TS-HDS IgM levels of 30 FMS patients and 21 healthy controls were evaluated by enzyme immunoassay. The anti-TS-HDS IgM mean ± SD levels of the patients in the fibromyalgia syndrome group were 7.7 ± 5 U/ml, and 13.2 ± 8.6 U/ml among the control group (P = 0.013). This significant reduction was analyzed by Student's t-test

IgM = immunoglobulin M, TS-HDS = trisulfated-heparin-disaccharide (TS-HDS)



In recent years, several studies suggested that SFN may co-exist with FMS. The innovative study by Üçeyler. et al. [16] was the first to demonstrate the coexistence of SFN in small FMS patient groups. These findings were later confirmed by larger scale studies that demonstrated a significant overlap between these two disorders [17-21]. As both disorders have common peripheral symptoms and possible common genetic association, our current finding regarding the potential association of anti-TS-HDS IgM to FMS might be the missing puzzle of the disorder's coexistence, although further study should be done to evaluate this linkage.

TS-HDS is the most common disaccharide part of heparin oligosaccharides and is found in heparan sulfate glycosaminoglycans which are present in peripheral nerves. The literature regarding anti-TS-HDS IgM is sparse. IgM binding to IdoA2S-GlcNS-6S, a trisulfated heparin disaccharide (TS-HDS), was first described by Pestronk and colleagues [22] as a high titer immunoglobulin found in five patients with polyneuropathy. In those studies, the authors suggested that heparan sulfate glycosaminoglycans interact with various growth factors in the peripheral nerves and might have a role in repair and maintenance. In 2012, Pestronk and colleagues [23] published another study on 99 patients assessing the clinical features of positive anti-TS-HDS IgM polyneuropathies compared to negative anti-TS-HDS IgM polyneuropathies. The authors found that positive anti-TS-HDS IgM polyneuropathies might be related to painful, mainly sensory, non-length polyneuropathy, with a higher prevalence of serum IgM M-proteins, capillary pathology, and persistent hand discomfort. Later studies confirmed some of these associations [11,12,24]. Several studies have recently evaluated the presence of abnormal levels of anti-TS-HDS IgM among patients with SFN as 28-42% [11,24,25]. Trevino and Novak [25] described abnormal high anti-TS-HDS IgM levels as associated with orthostatic, vasomotor, sudomotor, urinary, gastrointestinal, and sexual autonomic dysfunction. Levine and co-authors [11] demonstrated an association of abnormal high anti-TS-HDS IgM levels to acute-onset SFN. Zeidman and Kubicki [24] noted a high prevalence of neuropathic pain among seropositive SFN patients as their predominant symptom was widespread pain.

To the best of our knowledge, the study by Malik and associates [12] is the only study that evaluated the association of anti-TS-HDS IgM with FMS. The study included 22 patients with FMS and 2339 controls who underwent neuropathy evaluation. Their study showed a higher, but not significant, rate of abnormal high antibody levels among FMS patients compared with the control group (23% vs. 16%, respectively; P = 0.41).

We suggest a possible association between anti-TS-HDS IgM and FMS. We have found significantly lower levels of this antibody among FMS patients compared to healthy controls. In addition, in contrast to previous studies evaluating this autoantibody, we examined the antibody levels as a continuous variable rather than normal or abnormal levels. Interestingly, previous studies have described abnormal high levels of the antibody associated with certain medical conditions, while we found a significant association with lower anti-TS-HDS IgM levels to FMS.

The relation between anti-TS-HDS IgM and FMS is unclear. A possible mechanism may be related to the role of TS-HDS in maintaining peripheral nerves physiological function, as suggested by Pestronk and colleagues [22]. FMS has several peripheral nerve-related symptoms, including widespread pain and paresthesia [4]. This possible relation is hard to settle with the hypothesis suggested by Yunus et al. [5] and Clauw et al. [6] that FMS is a centralized pain syndrome. According to this theory, there is an augmentation of pain and of sensory processing in the brain, a connectivity decrease of anti-nociceptive brain regions, and an increased connectivity to pro-nociceptive areas [6]. However, the possible peripheral role of anti-TS-HDS IgM may further strengthen the concept of FMS as a dysautonomia-related neuropathic pain syndrome, as suggested by Martínez-Lavín et al. [7]. The presence of abnormal levels of anti-TS-HDS IgM among SFN patients, a peripheral nerve system disorder, may also support this concept [11,24,25].

LIMITATIONS

There was a significant age difference between the study groups. Although men are a minority among the FMS patient population, they were not represented in our research. Moreover, this

analysis is a cross-sectional study and therefore does not evaluate how auto-antibody levels change over time and how they influence patient symptoms and conditions. In addition, due to our relatively modest number of patients, further larger-scale studies should be performed to comprehensively understand the association found in this study.

CONCLUSIONS

There is a possible association of anti-TS-HDS IgM with FMS. This finding might support the hypothesis that FMS is a dysautonomia-related neuropathic pain syndrome, and autoantibodies to neuronal elements might have a pathogenic role in its pathogenesis.

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CONFLICT OF INTEREST

Harald Heidecke is the owner of CellTrend GmbH, Luckenwalde, Germany.

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Simplicity is the final achievement. After one has played a vast quantity of notes and more notes, it is simplicity that emerges as the crowning reward of art.

Frédéric François Chopin (1810–1849), Pianist and composer

The thing that makes you exceptional, if you are at all, is inevitably that which must also make you lonely.

Lorraine Vivian Hansberry (1930–1965), playwright and painter