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Autoantibodies in Females Exposed to Indoor Air Dampness Microbiota and Complaining of Electromagnetic Hypersensitivity-The Case Control Report

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ABSTRACT

We hypothesized that prolonged or cumulative exposure to indoor air dampness microbiota in moisture-damaged buildings and daily exposure to wireless telecommunication devices would potentiate the risk of electromagnetic hypersensitivity (EHS), which is poorly defined.

We performed a nested comparative analysis within an age- and sex-matched study of females who were exposed to dampness microbiota with self-reported complaints compatible with EHS (n=11). Their levels of autoantibodies towards 13 different autoantigens were measured.

EHS presented as multiple chemical sensitivity, profound fatigue, memory disturbances in all subjects (11/11), and cognitive impairment in the majority (9/11). When comparing the patients to controls, no difference was detected between the levels of the following autoantibodies: angiotensin II type 1 receptor (AGTR1), endothelin receptor type A (ETAR), adrenergic receptors α1AR, α2AR, β1AR, β2AR and cholinergic muscarinic receptors m1AChR, m2AChR, m3AChR and m5AChR. In contrast, IgG levels towards m4AChR and fibroblast growth factor receptor 3 (FGFR3), and IgM autoantibodies against glycosylated moieties of heparan and heparan sulphate (TS-HDS) were significantly decreased in the study cohort, $p=0.008$; $p=0.032$, $p<0.001$, respectively.

This is the first report demonstrating an imbalance in the nervous system autoantibodies in patients with EHS. The clinical significance of these altered responses remains to be clarified.

Keywords

Autonomous nervous system

Dampness and mold hypersensitivity Syndrome (DMHS)

Sick building syndrome

Autoantibodies

Neurological symptoms

Electromagnetic hypersensitivity

Research Article

HIGHLIGHTS

- Hypersensitivity to electromagnetic field (EHS) is an emerging yet poorly studied clinical entity.
- EHS is associated with multiple chemical sensitivity, profound fatigue, memory, and cognitive impairment.
- Neurologic manifestations may be explained by an imbalance of the autonomous nervous system.
- Determination of autoantibodies towards neuroreceptors and other self-antigens is a useful tool when clarifying the pathogenesis of EHS.

LIST OF ABBREVIATIONS

α1AR, α2AR, β1AR, β2AR: adrenergic receptors

AGTR1: angiotensin II type 1 receptor

CAT: catalase

DMHS: dampness and mold hypersensitivity syndrome

EEG: electroencephalography

EMF: electromagnetic fields

EHS: electromagnetic hypersensitivity

ETAR: endothelin receptor type A

HRV: heart rate variability

FGFR3: fibroblast growth factor receptor 3

IBS: irritable bowel syndrome

IFN-γ: interferon gamma

IL-2, IL-6: interleukins 2 and 6

GPCR: G-protein coupled receptors

GSH: reduced glutathione

MCS: multiple chemical sensitivity

MDA: malondialdehyde

m1-m5AChR: cholinergic muscarinic receptors

PCO: protein carbonyl

POTS: postural orthostatic tachycardia syndrome

SFN: small fiber neuropathy

SOD: superoxide dismutase

TNF-α: tumor necrosis factor alpha

TS-HDS: glycosylated moieties of heparan and heparan sulphate

VGCC: voltage-gated calcium channels

INTRODUCTION

For more than 50 years, individuals exposed to electromagnetic fields have complained of many different symptoms. The impact of electromagnetic fields (EMF) on the well-being of humans, animals and cell lines has been extensively studied, especially in the former Soviet Union and the Warsaw Pact countries. For example, in 1970, a report from the Soviet Union described a "microwave syndrome" experienced by military personnel working with radio and radar equipment; these people suffered diverse symptoms such as fatigue, dizziness, headaches, problems with concentration as well as memory and sleep disorders. Similar symptoms were observed in the 1980s in Swedes working in front of cathode ray tube monitors, and in some Finns who were exposed to EMF. The reported symptoms were reddening, burning, and tingling of the skin, especially on the face, as well as headache, dizziness, fatigue, and photosensitivity. These symptoms have been given the name of electromagnetic hypersensitivity (EHS) [1] or "microwave disease".

The number of people suffering from EHS in different countries seems to be growing and often it seems that EHS is associated with a hypersensitivity to many chemical substances, the Multiple Chemical Sensitivity (MCS) and / or other environmental sensitivities (Sensitivity Related Illness) [2]. In population studies, the prevalence of EHS has ranged from 1.5 percent in Sweden to 13.3 percent in Taiwan [1].

EHS is a phenomenon that evokes a wide range of non-specific symptoms in many organs, including both acute and chronic inflammatory processes in the skin and nervous system as well as in the respiratory, cardiovascular systems, and musculoskeletal systems. The symptoms may be related to a single EMF source or from a combination of multiple sources [2]. According to Valtonen [3], exposure to microwaves can cause various neurologic symptoms, such as sleep disturbances, insomnia, headaches, depression, fatigue, sensory changes, attention disorders, memory changes, dizziness, irritability, anorexia, anxiety, nausea, burning and tingling, sensations in the skin and EEG changes. EHS may manifest as mastocytosis involving infiltration with mast cells and their degranulation products that penetrate into the epidermis layers of the skin, as well as mediators of anaphylactic reactions such as histamine, chymase, and tryptase [2]. In a Finnish study [3], EHS developed in a proportion of patients who have a history of chronic exposure to indoor air dampness microbiota. EHS is a hypersensitivity presenting as an aggravated reaction to external environmental stimuli; it is a continuum of different hypersensitivities, or tolerance breaches with some of its manifestations attributable to neuroinflammation [4].

The entire topic of EHS has been complicated by the adoption of inappropriate models of provocation tests leading to erroneous interpretations such as an accentuated reaction of fear and worry, the so-called conversion symptom, or psychosomatic phenomena [5]. In some provocation studies, EHS patients have been unable to distinguish an active radio signal from a sham exposure by objectively detectable changes. In other studies, the experimental design has been improved, and changes in heart rate variability (HRV), erythrocyte damage, and impaired glucose metabolism in the brain have been identified, pointing to the presence of some sort of sensitization [1,6]. The effect of radio-frequency waves on the brain has been studied both objectively and accurately e.g., using various neuroscience techniques such as stereology, immunohistochemistry, and electron microscopy as well as approaches investigating cellular functions at the ultrastructural level but these have not currently been adopted into clinical practice [7]. The possibility that nonionizing radiation could exert non-thermal effects and thus represent a potential health hazard is not yet unanimously recognized [8]. In this scenario, radiation, probably in combination with other environmental factors, can trigger a low-grade inflammation [9]. Belpomme et al. tested different biological markers in approximately 450 patients with EHS as well as patients with combined EHS and MCS and control subjects. They found that no single biological marker would be elevated in all patients, but the combination of markers was suggestive of an insidious low-grade inflammation. It is noteworthy that in their studies the inflammation profile of their patients was similar to those with EHS and also to patients with combined EHS and MCS [9]. Long-term *in vivo* and *in vitro* exposures to mobile phone frequencies have been reported to be able to trigger the production of reactive oxygen radicals, creating a stressful oxidative and nitrative milieu in the tissues [10,11]. These exposures may also cause DNA damage through epigenetic and genetic changes. Electromagnetic radiation can interact with the cell's plasma membrane, evoking calcium flux from cell membranes, increasing the expression of stress proteins such as Heat Shock Protein (HSP), influencing melatonin and ornithine metabolism and disrupting the blood-brain barrier [12].

Many theories have been postulated as the underlying mechanisms, although none of them are capable of accounting for all the symptoms. Low-frequency electromagnetic fields may be able to activate voltage-gated calcium channels (VGCC) that are distributed at very high densities throughout the nervous system and play crucial roles in the release of neurotransmitters and neuroendocrine hormones [10]. Thus, it could be hypothesized that calcium channel blocking would be able to antagonize the effects of EMF. We also hypothesize that changes in cellular plasma membrane potential and in the activity of Na/K ATPase may occur in EHS patients as one important factor for patients with Chronic Fatigue Syndrome (CFS) [13]. Nocturnal cardiac dysautonomia was recently reported in CFS patients [14]. Since EHS patients self-report complaints compatible with dysautonomia, we deemed it appropriate to investigate the levels of their autoantibodies to autonomic nervous system receptors and other antigens in comparison with age- and sex-matched controls.

MATERIALS AND METHODS

Patients and matched controls

Initially, we collected sera from 42 individuals who had been exposed to dampness microbiota as well as 38 age- and sex-matched controls. We analyzed autoantibodies in 25 patients and 25 respective controls [15]. Out of these, we selected a subgroup of 11 patients with self-reported EHS and 11 respective controls. The patients replied to the extended questionnaires via Google Forms. We collected data about their demographics, social status, and a history of their exposure to dampness microbiota and to strong EMF, their co-morbidities, conditions that might have a confounding effect on the results such as silicone breast implants, tattoos, smoking, their own personal and family history of autoimmune diseases and current medication, etc. (Table 1). Additionally, we assessed their disease according to the criteria elaborated by Valtonen [3].

The patients were enrolled from the whole of Finland via social media; some of them had participated in our earlier studies. The inclusion criteria for the subgroup and the controls have been reported earlier [15]. Here, we examine the findings only for the subgroup of patients with self-reported EHS.

Clinical diagnosis of EHS

The electromagnetic field (EMF) in the patient environment cannot be measured routinely because it is difficult to assess objectively. Moreover, the abundant occurrence of microwaves is only a risk factor. At the individual level, the reaction to microwaves is very variable. Living or staying near 4G or 5G base stations, power lines, etc. is thought to be a risk factor for EHS. The diagnosis of EHS can be made if the patient reports the following symptoms:

1. When talking on a cell phone held close to the ear, the area around ear and cheek begins to become warm and reddens, it feels swollen, itchy, and have a burning sensation. Similar skin symptoms may appear in the hand holding the cell phone.

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Table 1. EHS group characteristics	
	EMS-Cases (N=11)
Age (Years)	
Mean (SD)	46.5 (9.05)
Median [Min, Max]	49.0 [34.0, 63.0]
Sex	
Female	11 (100%)
Body mass index (kg/m^2)	
Mean (SD)	27.5 (4.87)
Median [Min, Max]	26.7 [21.0, 38.0]
Water damage building exposure (Years)	
Mean (SD)	15.7 (6.12)
Median [Min, Max]	15.0 [8.00, 29.0]
Smoking status	
Negative	11 (100%)
City size (People)	
<50,000	4 (36.4%)
50,000-100,000	1 (9.1%)
>100,000	6 (54.5%)
Tattoo	
Present	1 (9.1%)
Breast implants	
Absent	11 (100%)
Human immunodeficiency viruses	
Negative	11 (100%)
Abdominal surgery	
Gynecology surgery	3 (27.3%)
Hernia	1 (9.1%)
None	7 (63.6%)
Family history of autoimmune diseases	
Positive	7 (63.6%)

2. Working with a laptop or wireless display terminal causes headaches, difficulties in concentrating and "brain fog", as well as fatigue. The patient may report headaches, nausea, eye pain and dryness, blurred vision, tingling. He or she may experience a tingling sensation and swelling at the distal ends of fingers.
3. While staying in spaces with heavy wireless technology, symptoms such as nausea, headaches, and fatigue, may appear.
4. Finally, the symptoms will be relieved by avoiding the above-mentioned functions or moving away from the location with high EMF or if the patient can be protected from a strong EMF, e.g., by using protective shielding clothing and devices, and not spending any time in an area with Wi-Fi and wireless telecommunication technology.

During the initial phase, the symptoms tend to disappear when the use of the mobile phone or display terminal is stopped, but the symptoms often reappear and are usually more intense when the individual returns to use these devices. After prolonged exposure, the symptoms may no longer disappear, complicating the diagnosis of EHS. Should the EHS become prolonged, it often worsens and later almost any electrical device can aggravate the symptoms. Usually, the patient reports that symptoms may start already after 15 min. The symptoms may begin to subside gradually, but the time needed for recovery is based on individual reactions. Often after the exposure to electrical equipment or EMF, the patient feels unwell for several hours. The problem of undiagnosed and untreated EMS has become even more serious as there is an on-going expansion in the numbers of 4G and 5G base stations. This may result in a situation that a patient may not be able to achieve relief from his/her symptoms even if he (she) stops using a cell phone and/or computer. In these cases, it would probably be useful to measure the EMF in the patient's domestic and employment environment.

Venipuncture, sample shipment and storage

The patients attended their local clinical laboratories or contacted our clinicians' offices where venous blood was withdrawn into three 9 mL vacutainer tubes. The blood was centrifuged after 30 min at 3000 g and the serum fraction was divided into 3 aliquots and sent overnight at room temperature to the Pathology Department of Lapland Central Hospital where the aliquots were stored at – 80°C until retrieved and sent on dry ice for autoantibody analyses to CellTrend GmbH, (14943 Luckenwalde, Germany).

Determination of autoantibodies with ELISA

Altogether we analyzed 13 autoantibodies: The IgG-class anti-adrenergic receptors (α1, α2, β1, β2), cholinergic anti-muscarinic receptors (m1-m5), fibroblast growth factor receptor 3 (FGFR3) and IgM-class antibodies to the glycosylated moieties of heparan and heparan sulphate (TS-HDS) autoantibodies. These were detected with the CE marked *For Research use only* commercial ELISA kits whereas anti-endothelin receptor type A (ETAR) and anti-angiotensin II type 1 receptor (AT1R) autoantibodies were detected with the CE marked *For in vitro diagnostics* ELISA kits (CellTrend GmbH). Each sample was analyzed in duplicate and the respective optical densities were read against the calibration curve constructed from the defined

sample in five dilutions. The level of autoantibodies for each sample was expressed as arbitrary units/ml. The ELISA methods were validated according to the FDA's "Guidance for industry: Bioanalytical method validation" https://www.gmp-compliance.org/guidelines/gmp-guideline/fda-guidance-for-industry-bioanalytical-method-validation

Statistics

Initially, metric variables were plotted and tested for normality. Thereafter, all variables were assessed by descriptive statistics as follows: number (percentage); mean (SD) or median (minimum, maximum) and stratified by study group. Paired Wilcoxon Signed Rank Test with exact p-values were applied in the comparisons of metric variables between EHS and controls. Spearman's correlations were calculated for the metric variables. Due to the exploratory nature of the study, no correction for multiple endpoints has been applied. All tests were 2 tailed with $P<0.05$ marking statistical significance, analyses and plots were made with R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

RESULTS

Demographics, family history and exposure data

The mean age of the patients was 46 years (min 34 - max 63), all were females. The average age of the corresponding controls was 45 years old (min 30 - max 62). None were obese or smokers, they lived in small or large cities; only one reported having a tattoo, none had silicone breast implants, none were HIV positive, 7/11 had not undergone any type of abdominal surgery, 7/11 had a positive family history for autoimmune diseases.

In addition to the prior exposure to dampness microbiota that was reported by all participants, 6/11 (54.5%) of the patients had lived or were living at less than one km from antennas and base stations (2G, 3G, 4G technology) during the last 10 years; and 3/11(27.3%) reported an exacerbation of their symptoms. None of the individuals reported using protective shielding clothing all or part time but 2/11(18.2%) had installed shielding material in their homes (e.g., Faraday Cages) to protect themselves against EMF; and 1/11 (9.1%) had moved to another home to avoid the strong EMF in their previous residence. The EMS influenced the patient's socio-economic status: one had become unemployed and two had to change their profession or workplace due to EMS.

The following symptoms were reported: 1. Reactions in the cheek and the ear area (reddening, swelling, itching, or burning sensation) during cell phone use - this was reported by 3/11 (27.3%), 2. The symptoms in distal fingers were experienced by 8/11 (72.7%) when speaking on the cell phone; 3. CNS and peripheral nervous system symptoms such as "brain fog", fatigue, headache, concentration problems during work with wireless equipment such as e.g. laptops, tablets, e-readers, etc. – these were reported by 8/11(72.7%). Symptoms were reported in 7/11(63.6%) during their stay in an extensive wireless internet network (Wi-Fi) or in an environment with a wireless local area network (WLAN), such as airports, railway stations, inside trains. The symptoms appeared on average 15 min after the exposure in 10/11 (90.9%) with a symptom duration of several hours in all 11 respondents; all patients reported that when they moved away from the WLAN environment or stopped the use of wireless devices then there was an abatement of their symptoms. A summary of the patients' characteristics is presented in Table 1.

The symptoms and co-morbidities reported by the patients

All patients reported concomitant MCS, fatigue, and memory impairment; 8/11 reported hair loss. Palpitations, syncope, somnolence, paresthesia, hyperhidrosis, thermoregulation problems, widespread pain, myalgias, auditory abnormalities were very prevalent. Postural orthostatic tachycardia syndrome (POTS), a sign of dysautonomia that was either physician-diagnosed or suspected was reported by about every second responder. The diseases and symptoms reported by patients and grouped according to the anatomical locations are illustrated in Figure 1.

Autoantibodies

There was no statistically significant difference between the levels of the following autoantibodies AGTR1, ETAR1, α1AR, α2AR, β1AR, β2AR, m1AChR, m2AChR, m3AChR, m5AChR when comparing the patients' levels with the corresponding levels in the controls. In contrast, the IgG levels against m4AChR and FGFR3, and IgM autoantibodies against TS-HDS were significantly decreased in the study cohort, $p=0.008$; $p=0.032$, $p<0.001$, respectively, Figure 2.

The levels of clusters of autoantibodies that were dysregulated were only moderately correlated; for example, the Spearman's correlation coefficient for IgM TS-HDS and IgG m4AChR was 0.63 ($p<0.05$) whereas for autoantibodies against FGF3, the correlation with other autoantibodies was in the range 0.52-0.56. The correlograms for all autoantibodies are presented for EHS and for the controls in Figures 3a and 3b, respectively.

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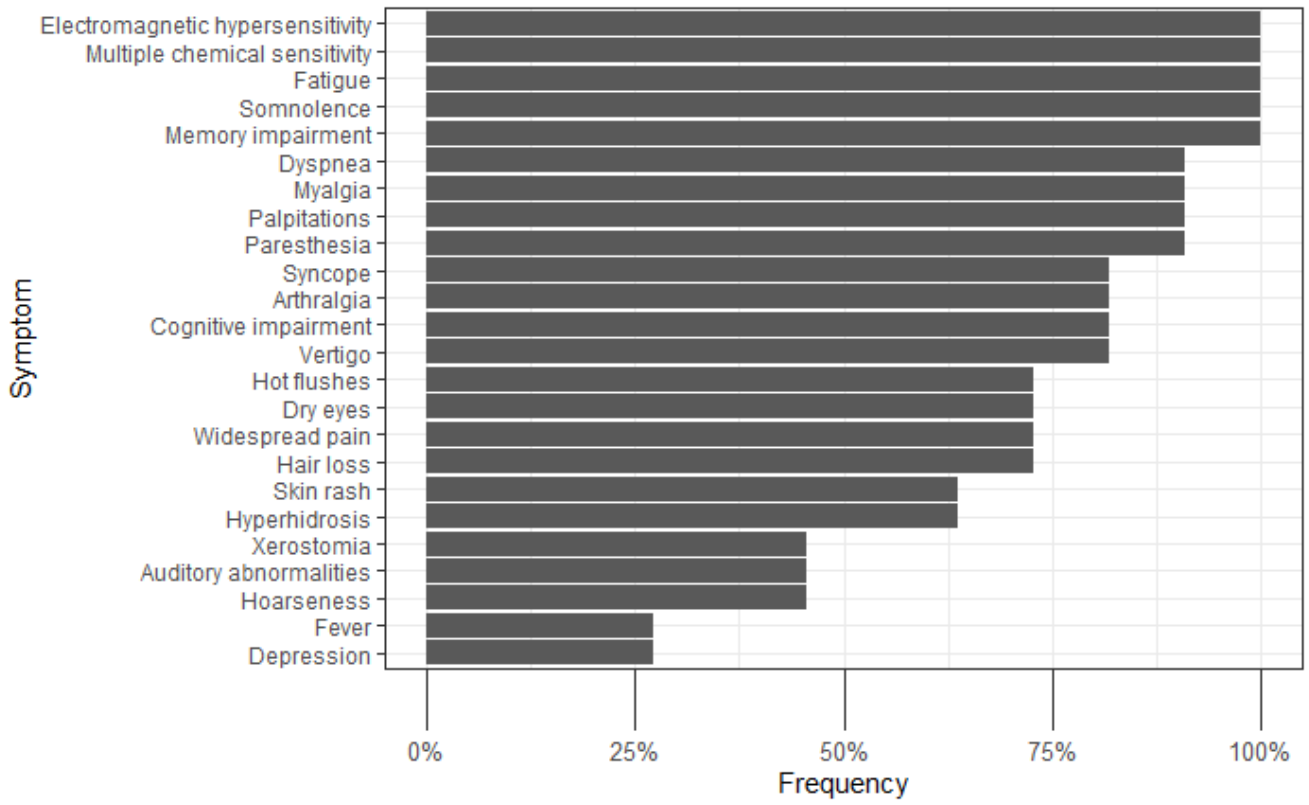

Figure 1: The prevalence of symptoms reported by the EHS patients.

DISCUSSION

Here, we present for the first-time, preliminary evidence that there is an imbalance of the autonomous nervous system in patients with self-reported EHS. We found a statistically significant reduction in clusters of autoantibodies such as IgG m4AChR and FGFR3, and IgM autoantibodies against TS-HDS. We also utilized the clinical criteria elaborated by Valtonen and found that this questionnaire was useful and simple in clinical practice; this is important as today there are no established and objective methods available with which to diagnose EHS [3].

One hypothesis on how to measure EHS has been proposed [6]; it was speculated that the measurement of bioregulation of the autonomous nervous system after the exposure to the EMF could be detected objectively. Furthermore, these investigators suggested that it would be beneficial to measure heart rate variability (HRV), electric skin potential and oscillation of the microcirculation, or capillary blood flow, functions all fundamentally regulated by the autonomous nervous system. The authors hypothesized that the fluctuation of capillary movements, the HRV and the electric skin potential would not be disturbed by the presence of an electromagnetic stimulus because healthy individuals have a good capacity for bioregulation. In contrast, patients with "genuine" EHS might have a deficit of bioregulation meaning that the normal oscillations in capillary vessels, electric skin potential and HRV would become disturbed because of an underlying disturbance of the autonomous nervous system. Here, we can provide convincing data showing that indeed there is an imbalance of the autonomous nervous system in patients with EHS.

Antibodies against FGF3 and TS-HDS have become a target of intense research. Recently, anti-FGFR3 has been linked to a broad range of neuropathies: in small and large fibers, sensory and motor fibers [16]. Several groups have reported that they found higher titers of anti-FGFR3 alone or in combination with anti-TS-HDS antibodies in patients with autoimmune small fiber neuropathy (SFN) [17-20], whereas others reported highly variable levels [19]. Unexpectedly, a significant reduction was obtained for IgG towards m4AChR and fibroblast growth factor receptor 3 (FGFR3), and IgM autoantibodies against glycosylated moieties of heparan and heparan sulphate (TS-HDS, $p= 0.008$; $p=0.032$, $p<0.001$, respectively). In the future, it would be of major practical and theoretical importance to examine the epidermal nerve fiber density from biopsies of

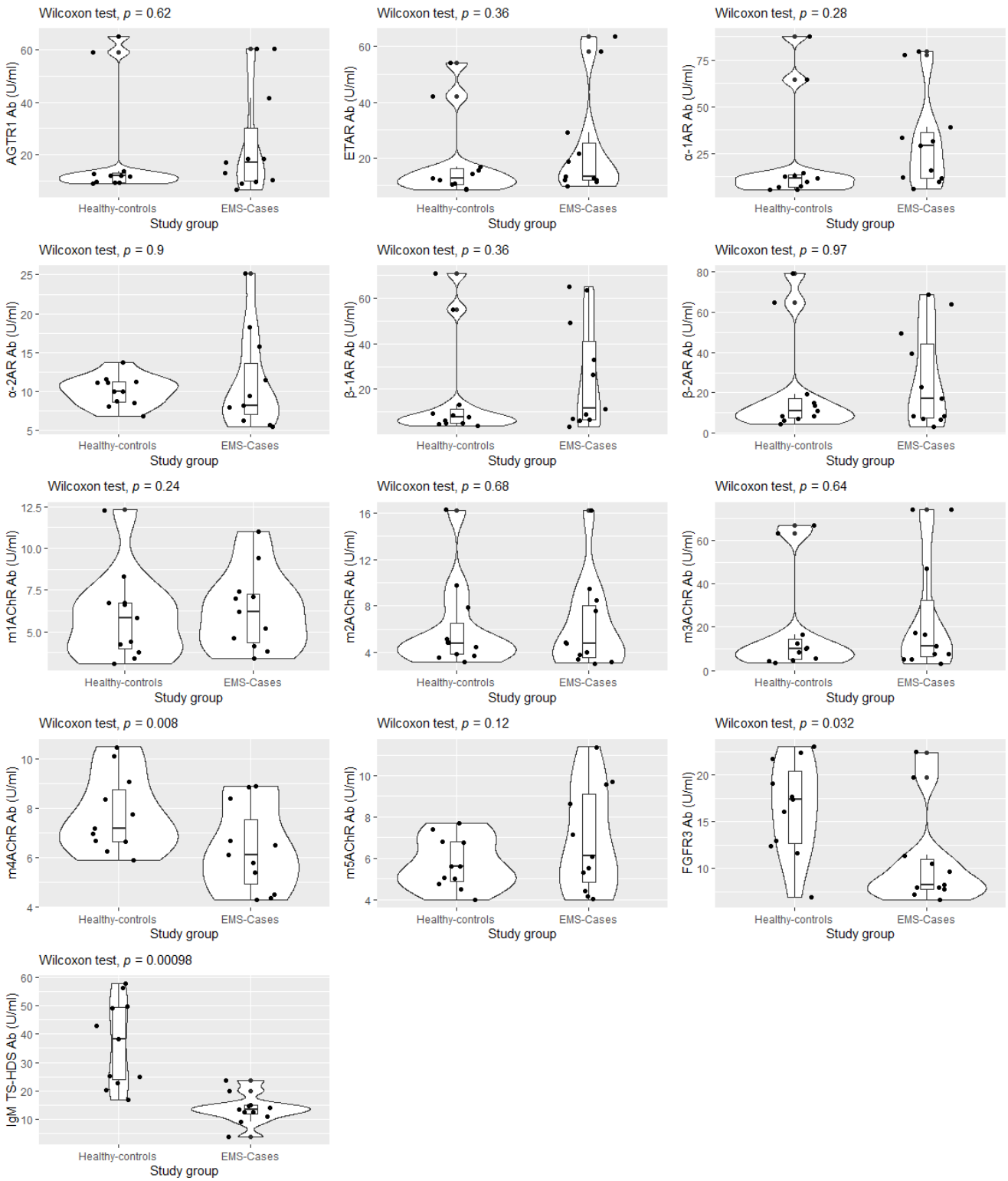

Figure 2: The comparison of the levels of all the autoantibodies from the EHS patient and the control groups.

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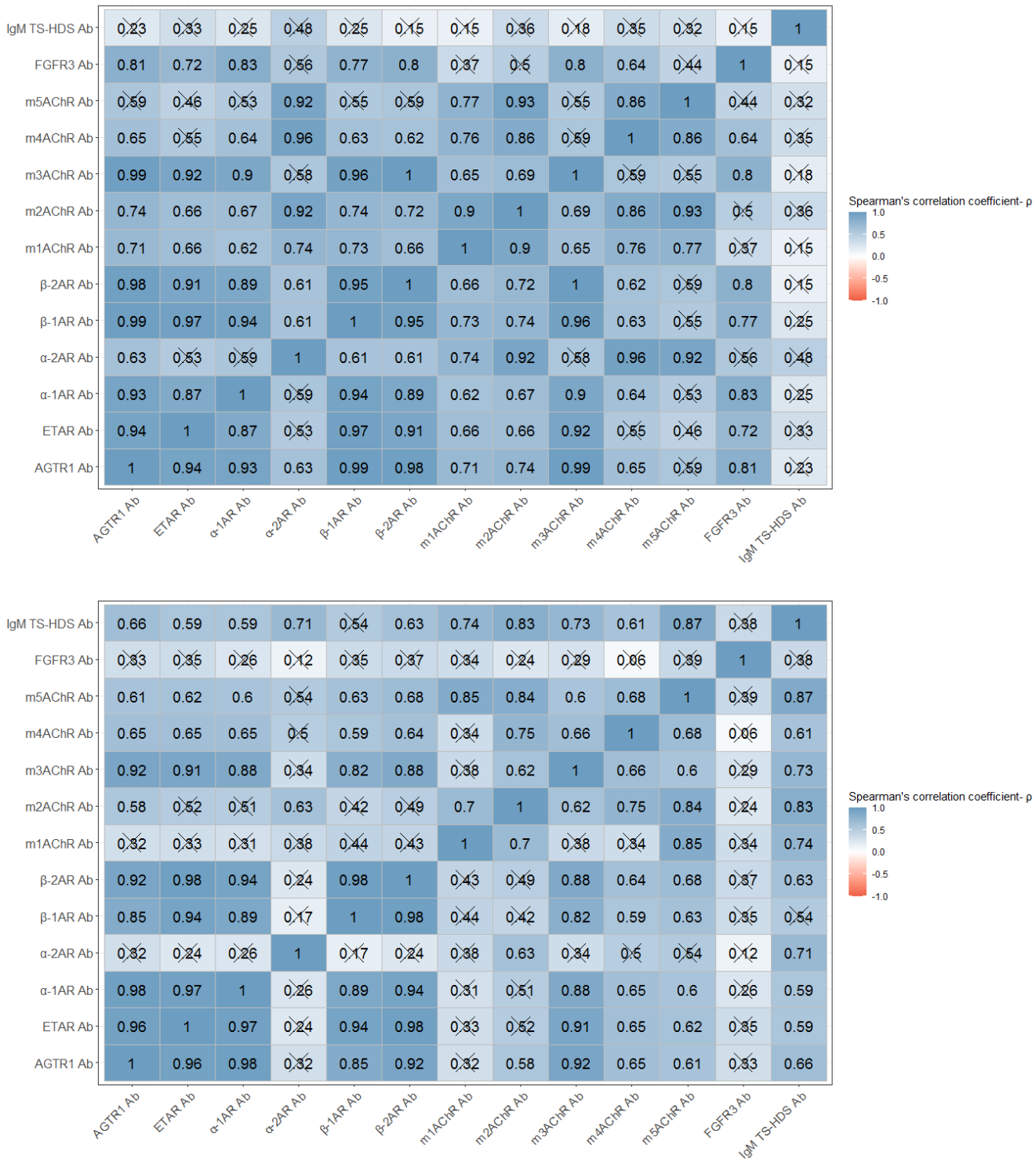

Figure 3: Correlograms of the autoantibodies; A) in the EHS patient group; B) in the control group. Non-significant correlations are crossed out with an X, significance was set as P<0.05.

these patients and to examine whether some of the reported symptoms such as increased hyperhidrosis, widespread pain are indeed manifestations of SFN. It would be also interesting to investigate the functions of these autoantibodies, i.e., whether they are stimulatory or inhibitory. These experiments could be conducted in recombinant cell lines that overexpress human receptors [21].

Cholinergic, adrenergic, endothelin and angiotensin II receptors belong to the superfamily of G-protein coupled receptors (GPCR). In recent years, the significance of these autoantibodies has started to be clarified. The presence of these autoantibodies in the sera of healthy donors means that they are a component of a natural network that has regulatory functions, and it has been speculated that they are a physiological part of the immune system. Their quantities correlate with autoantibodies against growth factors, growth factor receptors and signaling molecules. The signatures of these antibodies are age and gender dependent, and they may increase or decrease the expression of their target receptor on the cell membranes. Interestingly, GPCR and growth factors receptors are expressed not only by immune cells, but these proteins are also present in extracellular vesicles (exosomes). It is believed that it is the balance between these receptors and the coupling autoantibodies that maintains cellular homeostasis, cell migration and signaling [21].

A recent review on EHS summarized the available knowledge on the mechanisms causing this condition [22]. Here, combining our clinical experience and the laboratory data, we propose a preliminary hypothesis that might be an explanation of the immunopathology of EHS. Continuous or cumulative exposures to biological and chemical stimuli such as mycotoxins, particulate matter, volatile organic compounds produced by dampness microbiota in the indoor air result in an overstimulation of sensor receptors that leads to their hyperactivation. Sensory receptors are located on the afferent fibers of the peripheral nervous system. Direct penetration of xenobiotics through the disrupted brain blood barrier, or via the olfactory nerve or indirectly through circulating proinflammatory cytokines from the local inflammation can all be sources of neuroinflammation [23,24]. The "double trouble", i.e., the exposure to xenobiotics and non-ionizing radiation potentiates each phenomenon's effects i.e., acting in a synergistic manner to disturb the homeostasis of the (neuro)endocrine system. The combination of this kind of environmental overstimulation evokes a low-grade inflammation, impaired autophagy [24], the release of multiple autoantigens and their subsequent poor clearance, followed by the formation of neoantigens that may impact on the adaptive arm of the immune system [24]. These newly formed antigens together with fat soluble mycotoxins that have slow excretion kinetics may "behave" as so-called internal adjuvants causing a sustained hyperactivation of the immune system, resulting in an imbalance within the network natural autoantibodies. The reduction of the antibody levels (or their affinities as our ELISA technique measures simultaneously both components), as we have documented here, may lead to antibody compartmentalization, the formation of immune complexes or the exhaustion of plasma cells so that they are unable to produce antibodies. The imbalance of autoantibodies revealed in this study manifests as dysautonomia and this explains why our patients' reported symptoms of tachycardia, dizziness, POTS, palpitations, etc.

The limitations of our study are as follows:

1. We present data on a small cohort of patients with EHS;
2. The EHS was self-reported, e.g., the objective measurements suggested by Tuengler and von Klitzing [6] were not applied. In the future, it would be of major importance to use validated physiological measurements that are beyond voluntary control or autologous activity of the patient [6].

The strength of our study is that we present evidence of a imbalance in autoantibody levels as assessed by objective techniques.

CONCLUSION

In conclusion, EHS is an emerging but neglected pandemic of environmental hypersensitivity with a clinical presentation of autonomic nervous system dysregulation. This disease has not yet been unanimously recognized, probably because there is no single valid biological marker to demonstrate its presence [25]. More studies are urgently warranted to tackle the pathogenesis of EHS.

DECLARATIONS

Ethics approval and consent to participate

We obtained an approval from the Ethical Committee from the Northern Ostrobothnia, EETTMK 10/ 2020 to study biomarkers in patients exposed to dampness microbiota.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests.

Funding

No external funding.

Authors' contributions

TT, KV, GH, YS designed the study, KV and TT contacted patients and collected the data, KV collected and processed patient samples, KV applied for the ethical permission, GH, IK, performed statistics, HH performed laboratory testing, HA, AW, TT interpreted results, TT wrote the first draft. All authors approved the final version of the manuscript.

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Dedication

This work is dedicated to the sufferers from electromagnetic hypersensitivity (EHS) whose disease is not yet acknowledged by the medical profession.

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