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Interactions between radiofrequencies signals and living organisms

Electromagnetic hypersensitivity: The opinion of an observer neurologist

Hypersensibilité électromagnétique : Réflexions d'un observateur neurologue

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A B S T R A C T

Electromagnetic hypersensitivity (EHS) is a recent, uncertain and somehow confusing concept. It is now widely agreed that people claiming to be EHS really experience symptoms. However, no evidence for a causal link between the symptoms and electromagnetic fields (EMF) has been reported. Thus, we have to wonder whether EHS constitutes truly a relevant entity. Most of the previous studies suffer from methodological flaws. Owing to the quantification of symptoms, the interdisciplinary assessment of patients, and the use of personal exposimeters, the recent studies are of better quality. A set of convergent associated signs suggests that individual neuropsychic factors take a prominent, but maybe not unique, part in this condition.

R É S U M É

L'hypersensibilité électromagnétique (EHS) est un concept récent, incertain et déroutant. On admet aujourd'hui que les sujets EHS souffrent réellement de troubles subjectifs. Mais la preuve d'un lien de causalité entre les ondes électromagnétiques (OEM) et les symptômes n'a pas été faite. Nous devons donc nous demander si l'EHS est vraiment une entité clinique pertinente. La plupart des études anciennes présentent des défauts méthodologiques. La quantification des symptômes, l'approche interdisciplinaire des patients et l'utilisation d'exposimètres individuels ont permis d'améliorer les études récentes. Un faisceau d'indices concordants suggère fortement que des facteurs neuropsychiques individuels jouent un rôle important, mais peut-être pas exclusif, dans cette situation clinique.

1. Introduction

The term "Electromagnetic hypersensitivity" (EHS) was coined by Bergqvist et al. [1] in 1997 to gather in a unique concept the clinical conditions in which people complain of symptoms they attribute to an exposure to electromagnetic fields (EMF), such as those emitted by video display terminals (VDTs) or units (VDUs), power lines and/or electric appliances, and, later on, mobile phones and other wireless communication devices. More than ten years later, this concept remains uncertain, evolving and somehow confusing. The alternative term "idiopathic environmental intolerance (IEI) with attribution to electromagnetic fields (EMF)", proposed by World Health Organization (WHO) [2], did not help to clarify the question.

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The author of this opinion article had never had a direct medical practice of EHS subjects, but as a neurologist he attended many similar patients who complained of medically unexplained functional symptoms, such as headache, dizziness, sleep disturbances, memory troubles, fatigue, and so on. Thus, when he was asked to participate in bodies dealing with health effects of EMF, he focused his interest on the puzzling question of EHS. The scientific peer reviewed literature on the topic shows the great heterogeneity of the concept in terms of symptoms, sources of exposure, and also kinds of studies. Some of these studies, such as the provocation and population ones, tried insistently, but unsuccessfully to find evidence for a causal relationship between exposure to EMF and symptoms. This provides the opportunity to emphasize the difficulties, but also the importance of the clinical approach in conditions where there is a lack of pathognomonic biological or anatomical abnormalities. In such conditions, the relevance of the clinical inclusion criteria determines the validity of the complementary, experimental and epidemiological, researches. Therefore, a special attention will be paid, in this article, on the medical basic observations, i.e. the clinical descriptions and the associated factors and conditions. As there is often a gap between symptoms and organic lesions or disturbances, different approaches and points of view are to be collated and cross-checked.

The comments will turn seriatim on the clinical studies, the provocation studies, the epidemiological studies, the associated factors and conditions, and the treatment.

2. Clinical studies

The first descriptions of the self-reported electric and magnetic fields sensitivity were based on cases studies carried out in occupational settings and/or with small sized populations. In the 1980s, they concerned some nonspecific skin symptoms, mainly subjective (itching, burning, stinging and so on), attributed to a work near video display terminals (VDTs) [3] or visual display units (VDUs) [4]. In the 1990s, a general clinical portrait has been described in which neurasthenic symptoms, such as dizziness, fatigue, headache, difficulties in concentrating, etc., seemed to dominate, along with nonspecific skin disorders and ocular, gastrointestinal, or respiratory symptoms [5]. The common features of these self-reported health disorders were their acute occurrence when coming near electrical devices, including power lines, and their disappearance when the source was off or not nearby. However, no symptoms or combination of symptoms were recognized as pathognomonic for hypersensitivity to electricity. On account of the significant overlap in the symptoms reported to various EMF sources, the term of electromagnetic hypersensitivity was coined during a meeting of European experts [1] to include all these situations in the same entity. Symptoms associated with mobile phone use were described shortly after [6,7] and were also included in the syndrome. Later on, the clinical descriptions of this wide clinical entity were only qualitative, listing an increasing number of unspecific symptoms, up to 57 on the review of Irvine [8], and did not result in generally accepted diagnostic criteria, except the subjective attribution of symptoms to electric and magnetic fields by the subjects themselves, as pointed out by several reviews [8–10].

However, some authors continued to distinguish, at least partly, people with skin symptoms related to the use of VDTs from those with perceived hypersensitivity to electricity. In 1999, Hillert et al. [11] advanced that skin and not neurovegetative symptoms characterize the syndrome during the first years of illness. In his review of the literature, in 2002, Levallois [12] opposed clearly a dermatological syndrome and a general syndrome which associated skin disorders with a lot of non-specific symptoms present in other atypical syndromes such as multiple chemical sensitivity or chronic fatigue and seemed to have a worse prognosis. This difference in prognosis was confirmed the same year by Stenberg et al. [13] in a series of 250 subjects, 50 with hypersensitivity to electricity and 200 with VDT-related skin symptoms. The latter had a favorable prognosis, while most of the former, particularly women, experienced extensive medical problems of variable severity, ranging from very mild symptoms to major impairment resulting in increased work absences and eventually unemployment.

These data were not taken into account in the consensus reached at the end of the workshop on "Electromagnetic hypersensitivity" convened by WHO in Prague in October 2004: "*EHS is characterized by a variety of non-specific symptoms that differ from individual to individual. The symptoms are certainly real and can vary widely in their severity. For some individuals the symptoms can change their lifestyle. The term 'Idiopathic Environment Intolerance (IEI) with attribution to EMF' was proposed by the working group to replace EHS since the latter implies that a causal relationship has been established between the reported symptoms and EMF… IEI is a descriptor without any etiological implication.*" [14]. This change in terminology, which maintains the concept of a single entity, could be interpreted as a simple transformation of diagnosis criteria into the definition. In fact, its worth was to emphasize the lack of evidence of a causal relationship between exposure and symptoms. However, it did not contribute to a better understanding of the question and did not enter into practice.

Two later approaches have improved the clinical study of EHS. The first one consists in quantifying the symptoms and regrouping them in a small number of components, while the second one consists in gathering EHS subjects and patients complaining about other environmental illnesses into a single group, and subjecting all them to the same systematic interdisciplinary assessment.

To our knowledge, the first attempts to quantify the symptoms were those of Hillert et al. [11] and Hutter et al. [15], but the most complete work on this topic is that of Eltiti et al. [16]. On the basis of a pilot study, the authors developed a 57-item questionnaire and asked the participants to rate their current symptoms on a scale ranging from 0 (not at all), to 4 (a great deal), with the intermediate values of 1 (a little bit), 2 (moderately) and 3 (quite a bit). Questions regarding the relationship between symptoms and various EMF-producing objects, negative health changes around EMF and general health were also included. In a first study, the authors sent the questionnaire to a randomly selected sample of the general population and performed a principal components analysis of the data which resulted in eight subscales: neurovegetative, skin, auditory, headache, cardiorespiratory, cold related, locomotor, and allergy related symptoms. In a second study, the questionnaire was completed by 88 EHS individuals, 22 of whom took part in a retest and exhibited good test–retest reliability. The symptoms were regrouped into the eight subscales and, overall, good internal consistency was obtained for the subscales and the total symptom score. The EHS group had a significantly greater severity of symptoms than the control groups for all eight subscales and for the total symptom score, but with a continuum of symptoms severity ranging from individuals who experience mild or no symptoms to those with severe symptoms. A cutoff value of the total score between controls and EHS subjects was then defined by dividing the distribution in controls into three symptom severity groups using quartiles. So, a total symptom score $\geqslant 26$ (75th percentile and over) was considered as representing severe syndromes. By construction, 25% of controls were in this range. In the EHS group, they were 73%. In addition, 33 (37.5%) of the EHS individuals were found to suffer currently from a chronic illness, of whom 25 had a severe syndrome, while they were only 19.7% in the general population. Finally, the authors proposed the following criteria to identify EHS individuals: (1) a total symptom score greater than or equal to 26; (2) the individual explicit attribution of his or her symptoms to exposure to EMF-producing object(s); and (3) current symptoms cannot be explained by a pre-existing chronic disease. Using these criteria, 38 (43.2%) EHS individuals in study 2 would fit the profile of someone who is sensitive to EMFs. Some remarks can be addressed to this study. Neither ocular symptoms nor ocular subscale were extracted from the data by the principal components analysis, whereas ocular symptoms seem to be experienced by users of VDTs or mobile phone [17]. This leads one to wonder whether questions on ocular symptoms were included in the questionnaire. As a matter of fact, the authors acknowledged that it would be beneficial to replicate the forced eight-factor solution with a larger self-reported sample of EHS individuals to determine if there are any difference in the underlying pattern of symptoms between healthy and EHS individuals. Despite these limitations, this study laid down the bases of a reliable classification of the subjects reporting symptoms they believe caused by EMF, allowing to attenuate the heterogeneity and the difficulties resulting of a selection of EHS subjects only based on self-reported symptoms.

The quantification of symptoms was recently used by Rubin et al. [18] and Johansson et al. [19] for performing a reappraisal of the question of two separate entities within the frame of EHS. Both studies compared people reporting sensitivity to mobile phone and "electrosensitivity" (EHS) to people reporting only sensitivity to mobile phone (MP) and controls. In the first study, EHS subjects ($n = 19$) were found to experience greater depression, worse general health and a greater number of other medically unexplained syndromes compared to MP subjects ($n = 52$) or controls ($n = 60$). In the second one, the EHS group reported more symptoms than the MP group, the MP group reporting a high prevalence of somatosensory symptoms, whereas the EHS group reported more neurasthenic symptoms. These findings put again the question of whether there are two distinct entities under the vocable EHS or these two pictures correspond to two stages of the same phenomenon, a first one of mild intensity and good prognosis, linked with only one source of EMF (VDTs or mobile phone), and the second, more severe, linked to a range of EMF sources. Only carefully designed prospective studies can answer this question and, contingently, help to describe more precisely the relationships between the two entities.

Simultaneously, some other studies quantified also the symptoms reported by EHS individuals. Hillert et al. [20] used a 7-point Likert scale from 1 = not at all, to 3 = some, 5 = moderate, and 7 = very much, Thomas et al. [21,22] a 4-point Likert scale from heavy to moderate, barely, and not at all, for the acute symptoms and a 5-point Likert scale (nearly daily, several times a week, nearly every week, about once a month, seldom or never) for the chronic symptoms, whereas Berg-Beckhoff et al. [23] used several rating scales without indicating their mode of quantification. Furthermore, these different studies used questionnaires which are composed of different symptoms. In addition, none of them used data analysis methods, such as principal components analysis, in order to uncover semiautomatically the underlying structure of symptoms. Obviously, questionnaires, rating scales, and methods of analysis need to be harmonized to allow a fair comparison of the results, and also to undertake the multicentric studies which could be essential to answer the question to know whether the concept of EHS comprises only one or two separate clinical entities.

A quite opposite clinical approach to the EHS question is to include EHS subjects in a group of patients who had complaints which they themselves attributed to other environmental causes and to submit the whole to the same investigation procedure. This was carried out in the framework of a pilot research project conducted in Basel from April 2001 to May 2002 [24,25]. Sixty three patients took part in a threefold diagnostic approach, including a thorough medical examination, an extensive psychiatric exploration, and a careful environmental analysis. Then, an interdisciplinary case conference was performed, according to a strict procedure, to reach a consensus rating the extent to which the patient's general status was influenced by either medical, environmental, or psychological–psychiatric findings. Thus, about 50% of the symptoms could be attributed to psychiatric causes. Finally, the authors exploited the discrepancies between self-rating and experts' evaluation of psychological strain for creating four subgroups of patients. These subgroups were found to differ significantly in medical, psychiatric and environmental etiologies, personality traits and interactional competencies. However, exposure to electromagnetic fields, which was the most frequently alleged environmental cause of symptoms (26%), was not reported to be related neither to one or more of the subgroups, nor to a particular set of symptoms. This suggests that EHS could not be distinguished from other environmental illnesses. Although this study was likely too expansive in time and money to be widely spread, it deserves to be replicated and to inspire further researches on the similarities and differences between all the unexplained environmental illnesses.

In summary, for more than twenty years, the clinical studies of EHS suffered from methodological flaws, gave poor and contradictory results, and were unable to characterize this complex condition and design reliable diagnosis criteria. Although the concept of a single clinical entity was proposed twice, first by a group of European experts and later on by WHO, its validity was never firmly established. During the last three years, it has been shown that the clinical approach of EHS can be improved if it is based not only on the simple patient belief, but also on objective and complementary methods. These include the quantification of the symptoms and their regrouping into a few components, the use of personal exposimeters (see below), as well as a comprehensive assessment of the subjects and the comparison with other groups of patients. However, these different approaches need to be harmonized and coordinated in order to develop diagnostic tools widely accepted for care and/or research. Then, it should be possible to address the basic question which is how to consider the subjects attributing their symptoms to an EMF exposure. Do they form one or two specific entities or, on the contrary, are they to be included in larger concepts such as environmental disorders or, as discussed later on, unexplained medical syndromes? Anyway, none of these studies offered evidence for a causal relationship between symptoms and EMFs.

3. Provocation studies

On account of this lack of evidence from clinical studies, the so-called provocation studies were considered as the method of choice to investigate scientifically the actual sensitivity of the EHS subjects to electromagnetic fields.

Under experimentally controlled laboratory conditions, volunteers with self-reported EHS, often compared with matched controls, were exposed to 2 conditions, an active condition in which weak EMFs are presented and an inactive or sham condition in which they are not. Two outcomes can then be examined: the participant's ability to correctly discriminate active from inactive conditions (their electrosensitivity) and the participant's tendency to experience more symptoms during and after the active condition.

Even restricted to blind and double-blind studies, these experiments were numerous enough to allow three specific systematic reviews: Rubin et al. [26] in 2005, Röösli [27] in 2008, and Rubin et al. [28] in 2009.

In their first review, Rubin et al. [26] divided the studies according to the exposure conditions, into VDU-related provocation studies ($n = 13$), mobile phone-related provocation studies ($n = 7$), and others, mainly ELF-related studies, for patients with generalized EHS ($n = 11$). Overall, only 7 among these 31 experiments reported evidence supporting the existence of hypersensitivity. For 2 of these seven, the same research groups subsequently tried and failed to replicate their findings. In 3 more, the positive results appear to be statistical artefacts. The final 2 studies gave mutually incompatible results with one showing improved mood as a result of provocation [29], while the other shows worse mood [30].

In his review, Röösli [27] considered only the mobile phone-related studies and divided them into those exploring the participant's ability to discriminate active from sham RF-EMF exposure and those assessing the participant's tendency to experience more symptoms in the active condition. RF-EMF discrimination was investigated in 7 studies including 182 self-declared EHS individuals and 332 non-EHS individuals. The pooled relative difference between observed and expected correct choice of all studies was 0.042, with a slightly higher correct field detection rate for studies with EHS participants (0.07) compared to those with non-EHS participants (0.02). However, according to a meta-regression, neither type of study participants (EHS vs. non-sensitive), nor exposure source (mobile phone vs. base station) or exposure duration was associated with better performance in rating the correct field status. Two studies applied more than three provocation tests per individual in order to detect a possible small minority who are indeed able to perceive low level RF-EMF, and were unsuccessful. Thus, although a substantial part (56%) among EHS individuals claimed to be able to perceive radiofrequency EMF in their daily life immediately or within a few minutes after exposure [31], there is no evidence that EHS individuals could detect the presence or absence of RF-EMF better than other persons. Eight randomized trials, investigating 194 EHS and 346 non-EHS individuals, studied under laboratory conditions the effects of a short-term exposure to a mobile phone or to a base station on the occurrence of symptoms. They provided little evidence for such effects. On the contrary, some of these trials provided evidence for the occurrence of a nocebo effect: some severe reactions during sham condition [32], significant increase in the symptom score when EHS individuals were informed that they were exposed but not in controls [33], significant correlation between symptom score and perceived field intensity in both EHS and non-EHS individuals even though perceived fields were not associated with exposure levels [34,35].

The last review of Rubin et al. [28] is an update of that of 2005. It includes 15 new experiments, 5 of them being already taken into account in the review of Röösli. These new data did not change the previous conclusions. On the basis of 46 blind or double-blind provocation studies involving 1175 EHS subjects, the authors state that no robust evidence could be found to support the hypothesis that exposure to EMF is responsible for triggering symptoms in these subjects. Again, they underline the role of the nocebo effect in triggering acute symptoms in EHS sufferers.

In summary, despite their scientific appearance, the provocation studies do not allow us to close the debate on EHS. Many studies, particularly the earliest ones, included non-well-selected subjects, as pointed out in the first part of the present article. In addition, the exposure conditions were not always well-controlled [36]. These two defects could have reduced the power and the sensitivity of the studies, and thus masked some small effects. Therefore, only two firm conclusions can be drawn from these studies. The first one is that the large majority of EHS subjects who claims to be able to perceive low-level EMF are not able to do so under double-blind conditions in a laboratory. The second one is that, despite a possible lack of power, several studies were sensitive enough to observe a nocebo effect. Finally, the lack of subjective reaction to a short term EMF exposure does not mean that biophysical factors are not involved in the process of EHS. As a matter of fact, the provocation studies cannot address the question of the health effects of long-term continuous exposure to weak EMF. Epidemiological studies are more suitable for this last purpose.

4. Epidemiological studies

Population-based studies have been performed for studying the health effects of long-term exposure to base stations on well-being, health, and cognitive functions, but also for calculating the prevalence of EHS.

Epidemiological cross-sectional studies of subjects living near mobile phone base stations were performed in Austria [15], Egypt [37], and Germany [21–23,35]. Only one of them [37] compared EHS individuals with normal controls. Symptom questionnaires they used to assess the well-being of subjects were akin to those used for clinical EHS studies.

One of these cross-sectional studies [35] was similar to an experimental study, as the operator (T-Mobile GmbH) allowed the investigators to use a UMTS base station (2167.1 MHz, 20 W) newly installed on an office building over a period of 70 working days before connecting it to the network. The base station was randomly turned on and off double-blind for period of one, two or three days. Exposures measured in the offices ranged from 0.05 to 0.53 V/m (mean $= 0.10 \pm 0.09$ V/m). Among 300 employees, 95 (67 men and 28 women) fulfilled a symptom questionnaire morning and evening, when arriving at work and before leaving it, during at least 25% of the study days. In the evening, they were also asked on the on–off position of the base station during the day, and on the relation between this position and their symptoms. No evidence for a correlation between mobile phone base station exposure and self-reported health complaints was found. On the days when participants made significantly more health complaints, they also thought the base station was in use. This was interpreted as an incorrect attribution and underlined the importance of using double-blind designs in corresponding research. Due to the small number of participants, the study does not allow firm conclusion.

The others studies show clear-cut differences in aims, methods and results, particularly in the long-term EMF exposure assessment which is the major difficulty encountered in this kind of studies. Some used only one isolated measurement, carried out either at the time of questionnaire [15] or independently of it [37]. Hutter et al. [15] measured the field strength of high-frequency EMF in the bedrooms of 336 households and divided the results into 3 categories ($\leqslant 0.1$ mW/m^2; 0.1–0.5 mW/m^2; > 0.5 mW/m^2), for studying the effects on well-being, sleep quality and some cognitive tests, in 365 randomly selected inhabitants living for more than one year near to 10 selected base stations. There was no significant effect on sleep quality. Perceptual speed increased, while accuracy decreased insignificantly with increasing exposure level. Headache, cold hands or feet, and difficulties to concentrate were found to be significantly more frequent at higher exposure levels. However, this paper was considered to suffer from substantial methodological weaknesses. First, it was possible that the positive associations occurred by chance [38], as they disappeared after the implementation of a Bonferroni–Holm-Correction [39]. Moreover, the selection of test-subjects' addresses in relation to the location of the base stations did not take into account other environmental influences and therefore could have induce some cluster effects and false positive results [39]. Abdel-Rassoul et al. [37] found a significantly higher occurrence of headache, memory changes, dizziness, tremors, and sleep disturbances in inhabitants around a mobile phone base station ($n = 85$), compared to a non-exposed matched control group ($n = 80$). Here again a Bonferroni correction was not performed. Furthermore, 37 inhabitants living in a building under the base station and 48 living opposite the station were mixed to form the exposed group.

More recently, two different personal dosimeters were used, allowing either recordings of an exposure profile over 24 hours for three mobile phone frequency ranges [21,22] or measurements on four different positions on the bed of the participants during daytime (from 7 am to 8 pm) with an apparatus measuring 12 frequency ranges [23]. In both cases, a total field value was calculated with different methods. In the first study, Thomas et al. [21] assembled a random population sample of 329 adults living in four Bavarians towns and did not find any statistically significant association between the exposure and either chronic or acute symptoms. In the second study, Berg-Beckhoff et al. [23] selected people from a German nationalwide survey, and 3526 persons responded to a questionnaire. As in the study of Heinrich et al. [35], people who attributed adverse health effects to mobile phone base stations reported significantly more sleep disturbances and health complaints but, for the five health scores used, no difference in their medians was observed for exposed versus non-exposed participants. Despite the real improvement provided by the personal dosimeters, it is obvious that none of these studies assessed correctly the long-term exposure to EMF. Based on experience drawn from previous research, standardized procedures have been recently proposed to allow direct comparisons of personal RF-EMF exposures in different populations and study areas [40]. These procedures would improve, together with the harmonization of the clinical tools, the scientific quality and the explicative power of the epidemiological studies. Meanwhile, we cannot draw from the results any inference on the health effects of long-term continuous exposure to weak EMF taken either alone, or associated with high periodic exposure.

Likewise, no firm conclusion can be drawn from the studies on the prevalence of cases of self-reported EHS. This prevalence was usually reported to be lower or equal to 5%: 1.5% in Sweden [41], 3.2% in California [42], 5% in Switzerland [43], 4% in United Kingdom [16], 3.5% in Austria [44]. In Germany, the prevalence was reported to be distinctly higher: 8–10% [45], and 10.3% [46]. The fluctuations of these values according to time invalidate the alarmist extrapolation of Hallberg and Oberfeld [47] who neglected also to take into account the sources of variation inherent in these studies, such as lack of precise information on electromagnetic environment, differences in questionnaire design, methods of selecting the population, and response rate. The interest of mass-media in the possible hazards of exposure to EMF could also affect the results as suggested recently by a prevalence study of Mortazavi et al. [48]. In a country such as Iran, where mass-media did not provide no information on the topic, difference in self-reported symptoms were found between individuals who had used mobile phone, video display terminals or cordless phone, and others, in a student population.

The prevalence studies provided some clues on socio-demographic factors associated with EHS. This seems to be more frequent in women than in men [36,38,18], in middle-age persons than in young and elderly [36,38], and in persons with a higher education [38]. These results are partly inconsistent with those of the large-scale field study conducted by Blettner et al. [41] in a sample of 30 037 persons representative of the German population. In this study, the prevalence did not differ between men and women and was lower in participants with higher social status, as assessed by income and school education. Only the results in the middle-age persons were in agreement with the previous ones.

In summary, the epidemiological studies have provided till now uncertain and contradictory results. This results from obvious methodological defects, such as imprecise inclusion criteria and lack of reliable methods for assessing the long-term EMF exposure.

5. Associated factors and conditions

The lack of clinical criteria of diagnostic prompted also research aiming at identifying specific correlations which can be used as marker. Only the studies comparing groups of EHS subjects to controls in search of biological, functional, psychic and pathological correlates are considered here.

5.1. Biological correlates

Surprisingly, only few studies compared biological data obtained in EHS and control individuals. Furthermore, they reported very poor results. In a double blind provocation study, Lonne-Rahm et al. [49], who measured stress hormones in the blood (adrenocorticotrophic hormone, prolactin, neuropeptide Y, growth hormone), did not find any significant difference between patients with self-reported sensitivity to electricity ($n = 24$) and age- and sex-matched controls ($n = 24$), nor was there any effect on blood stress hormone from stress or exposure to electromagnetic fields from a VDU. In 14 people who reported a hypersensitivity to electricity including disabling fatigue, Hillert et al. [50] found no significant reduction in acetylcholinesterase activity in any subject, nor, in the group as a whole, at the time of severe fatigue, and no correlation between the reported degree of fatigue and the cholinesterase activity.

Recently, Belyaev et al. [51], Markova et al. [52], and Belyaev et al. [53], from the Department of Genetics, Microbiology and Toxicology of the Stockholm University, compared the effects of exposure to 50 Hz magnetic field and different mobile phone microwaves (MWs) on human lymphocytes from EHS and healthy persons. No significant differences in effects between the two groups were observed, except for the effects of UMTS MWs and GSM-915 MHz MWs on the DNA repair foci, which were more frequent in hypersensitive ($p < 0.02$[53BP1]–$p < 0.01$[gamma-H2AX]) than in control subjects. These results need to be replicated.

One issue remains controversial. It concerns the mast cell infiltration of the skin. A first histopathological study [54] assessed hyperplasia of sebaceous glands, occurrence of telangiectasia, intensity of inflammatory infiltrate, degree of hydropic degeneration of basal cells, occurrence of demodex folliculorum, degree of degenerative changes in elastic fibers and number of mast cells in 83 facial punch biopsies from patients with skin complaints with or without skin lesions and supposedly associated with work at VDUs, compared to 51 biopsies from subjects with no VDU exposure with or without lesions. No parameter was significantly more common in exposed subjects than in non-exposed persons with equivalent skin signs. However, a theoretical model based upon mast cells infiltration and histamine release in the skin was proposed by Gangi and O. Johansson [55] to explain the proclaimed sensitivity to magnetic fields in humans. These authors grounded their belief on their previous findings [56,57]. First, O. Johansson et al. [55] found an increased number of mast cells in the upper dermis, before and after an open-field provocation, in two screen dermatitis patients, as compared to normal healthy skin. In a second study, O. Johansson and Liu [57] observed that the normally empty zone between the dermo-epidermal junction and mid-to-upper dermis was not present in an EHS group and, instead, this zone had a high density infiltration of mast cells with cytoplasmic granules more densely distributed and more strongly stained than in the control group. However, a replication study of Lonne-Rahm et al. [49] did not find any change in mast cells, before and after provocation by stress and EMF from a VDU, in 24 patients and 24 controls. Subsequently, O. Johansson et al. [58] described again a migration of mast cells towards the uppermost dermis after an open-field 2–4 hours VDU exposure in 5 out of 13 healthy volunteers. Now, O. Johansson continues to strongly uphold his theory in a series of review articles [59–61] in which he gathers a lot of data and articles non-related to the question, but without supplying new original data and without discussing and even quoting the works of Berg et al. [54] and Lonne-Rahm et al. [49]. Due to his intense activity with the self-help groups, the question arises of undertaking a replication study to clear up unquestionably the problem.

In summary, biological factors are not likely to be significantly involved in the pathophysiology of EHS. However, the role of genetic factors remains to be further explored.

5.2. Functional correlates

Some of the studies in search of functional correlates are stimulation studies using electric currents or magnetic fields as stimulators, but they differ in their design from the above mentioned provocation studies, as it will be shown.

The only exception to this remark, concerning electric currents, is the NEMESIS project performed by Mueller et al. [29]: a typical double-blind provocation study (50 Hz EMF at 100 V/m and 6 microT, 10 sham and 10 exposed in a randomized sequence) found no difference between EHS subjects ($n = 49$) and controls ($n = 14$) neither in current perception, nor in the number and types of symptoms encountered during the test.

Quite different is the work of Leitgeb, Schröttner and coworkers [62,63]. On account of its specificity and originality, it deserves to be considered independently of the others functional studies. In a first paper, Leitgeb and Schröttner [62] proposed to introduce a clear separation of two different ideas: the electrosensibility or electromagnetic sensibility (ES) that addresses the ability to perceive electric or electromagnetic exposures without necessarily developing health symptoms, and the electromagnetic hypersensitivity (EHS) that refers to the development of health symptoms attributed to environmental electromagnetic fields exposures. They also formulated the hypothesis that a significantly increased electrosensibility is a necessary, but not sufficient precondition for EHS. They defined ES experimentally as the threshold of perception of a 50 Hz current applied to the forearm of volunteers. A special mobile measurement apparatus that allowed investigations at homes or workplace was developed. The delivered currents were less than 5 μA at the beginning and then increased linearly until the volunteer perceives the current flow. Measurements were performed six times with 3 min breaks between each. With the aid of mean values and standard variations obtained in 708 adults (349 men and 359 women) from the general population, they created an electrosensibility diagram for characterizing the individual's sensibility with regards to what is considered "normal" for the general population. In a second paper, Schröttner et al. [63] explored three groups of EHS persons selected (1) from members of an Austrian self-help group, (2) from Swedish responders to a newspaper call, and (3) from Austrian persons actively asking for investigation in their search for help. They showed that all EHS persons as a group differ significantly from the general population sample, but with a pronounced overlap with the normal range. Moreover, quantitative ES was quite different among the three groups: members of the self-help group exhibited a considerable overlap with the general population sample, while the mean values obtained in the two other groups differed significantly ($p < 0.001$) from those obtained in the general population sample. Compared with electrosensibility diagram, individuals of group 1 were only 21% to be classified sensitive or very sensitive, while individuals of groups 2 and 3 were so classified in 44% and 60% of the cases respectively. These differences between the EHS groups were not compared with any other feature of EHS and therefore are difficult to analyze. They could only suggest that the ratio of slightly impaired versus severely impaired subjects differs in the three groups. Nevertheless, this method seems easy to carry out and reveals differences between EHS and normal subjects. Even though some of its methodological aspects remain to be clarified and codified, it could be added to the above mentioned quantitative clinical approach in order to better characterize various EHS populations. It could also provide evidence for a hypothetic biophysical mechanism involved pathophysiology of EHS.

Transcranial magnetic stimulation (TMS) is a noninvasive widely used method for stimulating brain. It is based on the ability of a magnetic field of 1–2 Tesla to penetrate skull and meninges, and to induce an electric current in the brain tissues. This produces neuronal depolarization, generates action potentials and elicits, when applied to the dorsolateral prefrontal cortex, a motor response. Because the used magnetic fields are static while RF-EMFs are periodic, and because their strengths are incommensurably greater than those of the RF-EMFs used in the wireless communication technologies, this method cannot be employed for performing strictly defined provocation studies. Actually, TMS is a mean for investigating the functional state of the brain. This method was applied to compare EHS and control subjects by Frick et al. [64], Landgrebe et al. [65,66], from the Department of Psychiatry of the University of Regensburg. In a pilot study comparing an EHS group ($n = 30$) to two control groups, one with a low level of subjective complaints ($n = 28$) and the other one with a very high level of complaints ($n = 27$) [64], there were no significant differences between groups neither in detecting the real magnetic stimulus nor in the objective motor response. However, the EHS group differed significantly from the control groups by giving a higher number of false alarm reactions in the sham condition, resulting in a lower ability to differentiate stimulation and sham conditions, a finding which supports the hypothesis of a nocebo effects. In the same study, cortical excitability parameters, i.e. inhibition and facilitation, were measured with a classical paired-pulse TMS protocol, showing a reduced intracortical facilitation in EHS subjects compared to both control groups [65]. This study was replicated in 89 EHS subjects and 107 matched normal controls. Again, the EHS gave a higher number of false alarm reactions in the sham condition (60% versus 40% in the control group), whereas intracortical facilitation was reduced in younger and increased in older [66]. This subtle neurobiological alteration could be related to the increased psychic vulnerability which was evidenced in the same study (see below).

Another functional test, the spectral analysis of ECG recordings, provided also differences between EHS and normal subjects. The results have been replicated successfully by the same team, the National Institute for Working Life in Umea, Sweden. These authors carried out two studies [67,68] on the autonomic nervous system regulation explored by the circadian heart rate variability (HRV). In their first study, Sandström et al. [67] monitored ECG for 24 hours and the HVR analyses showed that the high-frequency component did not have the expected increase with sleep onset and during nighttime in the EHS group ($n = 14$) compared to the matched control group ($n = 14$). In the second experiment, Wilén et al. [68] performed a single-blind provocation study (30 min, 900 MHz GSM, $SAR_{1g} = 1$ W/kg) in 20 subjects with mobile phone related symptoms and 20 matched controls. A memory test and a critical flicker fusion threshold (CFFT) test, which is an old, quick and simple method for estimating the vigilance of the subjects by detecting the frequency which induces the fusion of flickering lights, were performed before and after the real and sham exposure periods. The cases displayed a shift in low/high frequency ratio towards a sympathetic dominance in the autonomous nervous system during

CFFT and memory tests, regardless of exposure condition. A further single-blind provocation study from Kim et al. [69] confirmed that exposure to RF emitted by CDMA phones (20 min, 835 MHz, SAR = 1.6 W/kg) did not have any effect on HRV in both EHS ($n = 18$) and control ($n = 19$) groups. On the contrary, changes in several frequency domain variables extracted from ECG Holter recordings were reported by Andrzejak et al. [70] in 32 healthy subjects during a 20 min call with a mobile phone (1800 MHz GSM, $SAR_{10g} = 0.48$ W/kg), compared to periods of 20 min before and after the telephone call. These changes did not concern ultra low frequency power, but included increases in very low frequency (VLF) power, low frequency (LF) power, and high frequency (HF) power, as well as a decrease in the LF/HF ratio. All these data prompt to further explore with other techniques a possible dysregulation of the autonomous nervous system in EHS subjects.

A last complex study, combining a provocation paradigm with a functional brain MR imaging, provided a neuronal basis to the placebo effects. Landgrebe et al. [71] exposed 15 EHS subjects and 15 matched healthy controls to a sham phone EMF and a heat as a control condition, while the perceived stimulus intensities were rated on a five-point scale. During anticipation of and exposure to sham mobile phone EMF, an increased activation in the anterior cingulate and insular cortices, the so-called "pain neuromatrix" involved in the emotional processing in pain, was seen in the EHS group compared to controls, while heat stimulation led to similar activations in both groups.

In summary, transcranial magnetic stimulation, spectral analysis of ECG recordings, and functional brain MRI have recently provided a body of data supporting the hypothesis that EHS subjects suffer from slight functional abnormalities of the nervous systems. This opens new prospects of investigation which deserve to be further studied by means of concerted programs involving clinically well-characterized EHS subjects, but also other methods of functional investigation. For instance, to our knowledge, none of the different EEG methods were applied to the comparison between EHS and normal subjects during the last ten years.

5.3. *Psychic correlates*

Poor psychosocial conditions [72] and stress factors [73] have been soon suspected to be associated to skin symptoms in VDT workers. However, conventionally defined psychiatric disorders, as assessed by the 12-items General Health Questionnaire, were not found to be more frequent in EHS subjects than in controls [73,20]. This last result was confirmed recently [18].

As far as personality traits are concerned, a first approach with the Eysenck Personality Inventory [20] did not report any difference between EHS subjects ($n = 40$) and controls ($n = 201$). A different result was reported by Bergdahl et al. [74]. Using a Swedish version of the Temperament and Character Inventory, these authors found some significant traits of vulnerability in subjects alleging abnormal sensitivity to either dental filling ($n = 26$) or EMF ($n = 33$), compared to controls. No significant differences were found between the two sensitive groups, suggesting that they are quite similar regarding personality. Furthermore, Brand et al. [25] included the Operationalized Psychodynamic Diagnostics test in their interdisciplinary approach, and observed significant differences in personality structure and conflict between their subgroups of patients with environmental-related disorders. Recently, A. Johansson et al. [19] assessed anxiety, depression, exhaustion and stress by using a large series of questionnaire in people with mobile phone (MP)-related symptoms and people suffering from a more generalized EHS syndrome. In comparison with the reference groups, the MP group ($n = 45$) showed increased levels of exhaustion and depression, but not of anxiety, somatization, and stress, while the EHS group ($n = 71$) showed increased levels for all the conditions except for stress.

In a recent thorough enquiry, assessing primary reason for using a mobile phone, psychological health, symptoms of depression, modern health worries, general health status, symptom severity, and the presence of other medically unexplained syndromes, Rubin et al. [18] observed that people reporting to be electrosensitive and sensitive to mobile phone ($n = 19$) experienced substantially greater depression and greater worries about various aspects of modern life, as well as a worse health status with regards to 9 of 10 categories of somatic symptoms, as compared with either healthy individuals ($n = 60$) or people who report only sensitivity to mobile phones ($n = 55$).

In a case-control study already quoted [66], Landgrebe et al. used a previously constructed 42-item questionnaire assessing EMF-specific cognitive strategies [75], and found that EMF subjects ($n = 89$) took more time for completing the symptom questionnaire ($p < 0.001$), felt they are different from others ($p < 0.001$), expressed more rumination on their symptoms ($p < 0.0001$), more intolerance against physical symptoms ($p = 0.04$), and more vulnerability ($p = 0.006$) than controls ($n = 107$).

Finally, on the basis of a systematic consensus rating of the etiological relevance of data obtained from their interdisciplinary approach, Brand et al. [25] estimated that about 50% of the symptoms reported by the patients with environment-related disorders could be attributed to psychiatric causes.

In summary, here again, recent well-designed studies, mainly based on quantitative assessment of the functional symptoms, provides a set of convergent findings which suggests that EHS subjects suffer from psychic, and infrequently psychiatric, abnormalities. These are consistent with the above discussed results of the functional tests. This upholds the hypothesis that neuropsychic factors are involved in triggering and/or influencing EHS, but without excluding an influence of other factors, such as biochemical and/or biophysical ones.

5.4. Associated pathological conditions

EHS symptoms are regularly accompanied by other illnesses. This association was first mentioned by books reporting the experience of some self-aid groups as those of Philips and Philips quoted by Irvine [8], or Nordström quoted by Schooneveld and Kuiper [76].

This was confirmed by Eltiti et al. [16]. In the first part of their study, which compared 50 EHS subjects with 261 controls, the frequency of chronic diseases was significantly higher ($p < 0.01$) in EHS subjects (32%) than in controls (14.6%). In the third part, 88 EHS subjects reported to suffer from a variety of chronic illnesses, including chronic fatigue syndrome (9.1%), diabetes (8.0%), back/spine/joint disease (6.8%), and deficient/overactive thyroid (4.5%). Thyroid dysfunctions were also identified by Dahmen et al. [77], as well as liver dysfunction and chronic inflammatory processes, in a small but remarkable fraction of EHS subjects who take part in a study comparing several clinical laboratory parameters in 132 EHS subjects and 101 controls. A purely descriptive study of the Dutch Electrosensitivity Foundation [76] found that over half of the 93 respondents reported that they were at one time diagnosed as suffering from burnout (16.0%), multiple chemical sensitivity (15.6%), fibromyalgia (13.6%), chronic syndrome fatigue (13.2%), repetitive strain injury (8.6%) or less frequently Pfeiffer's disease, metabolic disease, sick building syndrome, posttraumatic stress syndrome, Sudeck's disease.

The meaning of these associated illnesses is not clear. Are they only risk factors contributing to the occurrence of EHS? Or, when their symptoms are similar to those of EHS and cannot be related to a clearly identified disease, should they be integrated together with EHS into the unique concept of medically unexplained syndromes? Bergdahl et al. [74] showed that subjects with alleged abnormal sensitivity to either dental filling or EMF are quite similar regarding personality. More recently, Brand et al. [25] studied patients with environment-related disorders as a whole and found that a classification based on the discrepancy between subjects' self-rating and experts' judgment resulted in 4 subgroups which corresponded only partly with the environmental exposures. However, this study blended true exposures, such as carbon dioxide or radon, and hypothetical exposures, such as EMF. It would be very interesting to perform similar studies, but including patients with fibromyalgia, chronic fatigue disease, or other unexplained syndromes together with EHS subjects.

6. Treatment

A systematic review of Rubin et al. [78] in 2006 shows that there were only few therapeutic trials on EHS and that most of them were of limited quality. Among the 9 trials, only three were double-blind and randomized. Of these three, two were performed by the same laboratory to test the efficacy of attaching electric-conducting filters to the VDUs of office workers who reported hypersensitivity to their computer monitors [79,80]. The first study identified significantly greater reductions in skin tingling with the active filter than with the placebo, without any other difference between the two conditions. The second study tested a larger sample over a longer period of time but was unable to replicate the results. The last double-blind randomized controlled cross-over trial [81] compared the effects of dietary supplementation with antioxidant vitamins and minerals versus placebo in a group of 16 EHS subjects. No improvement was observed over time.

However, 4 trials with cognitive behavioral therapy (CBT) suggested that they could be more effective than providing no treatment. Their theoretical rationale was based on a supposed vicious circle according to which assumptions made by the EHS patients regarding the causes of their symptoms lead to feelings of anxiety and helplessness, maladaptive attempts to avoid situations in which EMF are likely to be encountered, and self-fulfilling expectations of additional symptoms when such avoidance is not possible. CBT was used as a way of encouraging patients to challenge these assumptions and to test non-EMF related interpretations and ways of coping with their symptoms. Only two of these studies were described as randomized. Three of them reported a significantly better outcome with CBT than with control conditions, while one reported no significant differences.

Finally, in a recent trial, Nieto-Hernandez et al. [82] tested whether providing EHS subjects who participated in a double-blind, placebo controlled provocation study, with accurate feedback about their ability to discriminate an active mobile phone signal from a sham signal had any impact on their subsequent symptom levels or their perceived sensitivity to mobile phones. Six months after the delivery of the information ("correct" or "incorrect" at detecting a mobile phone signal), no significant differences in the Sensitive Soma Assessment Scale scores or in symptom severity scores were found between individuals told that they were correct ($n = 31$) or incorrect ($n = 27$) in their ability to detect mobile phone signals in the provocation study. However, the bearing of this result is attenuated by the fact that the information was delivered several months after the experiment.

7. Conclusions

No evidence for a causal link between EHS symptoms and acute exposure to EMF has been yet reported. However, the reported symptoms are admittedly real and the health effects of long-term exposure remain unknown.

For long time, the researches on the topic were seriously flawed by an inadequate clinical approach and by a lack of reliable tools for assessing the exposure. Some improvements have been made recently. They include the quantification of the symptoms and their regrouping in a small number of components, as well as the availability of personal exposimeters.

Besides, some comparisons between EHS and control subjects revealed that the former display significantly more associated factors than the latter. These factors are biological (defects in DNA repair), biophysical ("electro-sensibility" as defined by Leitgeb and Schröttner), and mainly neuropsychic (autonomic dysregulation, alteration of the intracortical facilitation at transcranial magnetic stimulation, activation of the "pain neuromatrix" by sham EMF exposure which could provide a physiological support to the nocebo effect demonstrated by the activation studies, more psychic vulnerability at personality investigations, greater depressions, greater worries about various aspects of modern life, more rumination of symptoms, more intolerance against physical symptoms). They open new prospects on the mechanisms involved in triggering and/or influencing the course of EHS. It was also shown that EHS subjects suffer more frequently than controls from organic diseases, such as diabetes and thyroid dysfunctions, as well as from medically unexplained syndromes such as multiple chemical sensitivity, fibromyalgia, chronic fatigue syndrome, burnout, and sick building syndrome.

Now, two main issues should be explored.

First, we have to wonder whether EHS is a relevant concept. If not, should it be divided into two partly overlapping entities, one attributed to only one EMF source and the other attributed to several sources, or, on the contrary, inserted into a larger entity including not only the other environmental intolerances, but also other medically unexplained syndromes? EHS should not be further studied per se. It would be valuable to develop a clinical diagnostic tool which would allow one to address these hypotheses. This tool should be elaborated in collaboration, like the protocol recently proposed to conduct personal RF-EMF measurement studies [39]. It could be based upon the works of Eltiti et al. [15] and Leitgeb and Schröttner [61,62], which are the ones today to provide possible cutoff values to separate EHS from normal subjects.

Second, we have to wonder if individual neuropsychic factors are actually the main factors involved in triggering and/or influencing the course of EHS, as suggested by the number of such factors found to be associated with the EHS conditions, compared to the biological and biophysical factors. This required first to replicate some studies, especially those measuring the electrosensibility or using TCMS and fMRI, second to compare the neurobiological data with those of psychological investigations, and third to confirm all the findings according to the advances in neurosciences.

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