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Multiple Chemical Sensitivity: A Sickness of Suffering, Not of Dying. Descriptive Study of 33 Cases

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Abstract

Objective: We describe patients with MCS, the evolution of the Quick Environmental Exposure and Sensitivity Inventory (QEESI) score with a special focus on people whose fillings were removed. **Methods:** We have conducted a retrospective longitudinal cohort study in patients diagnosed with MCS and attended in the outpatient Internal Medicine department of the University Hospital of San Juan de Alicante, from January 1, 2008 to January 1, 2021. Sociodemographic, clinical, QEESI and treatment-related variables were collected. We performed descriptive and inferential analyses. Mixed linear models were used to analyze the QEESI. Calculations were carried out with an α error of 5%. **Results:** Thirty-three patients were included (72.7% women, mean age 56.2). MCS was mainly triggered by mercury (N = 20) and food

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intolerance (N = 22). The mean interval from symptoms onset was 120 months (SD 81.6). 114 QEESIs were analyzed: 82 (N = 17 without amalgams) and 32 (N = 16 with amalgams). In patients without amalgams, severity scores increased across all subscales except the masking index (vs. with amalgams). Mean scores for the group without amalgams (vs. with amalgams) were: chemical intolerance, 62.8 points (vs. 63.4 and 46.7); other intolerances, 52.7 points (vs. 62.8 and 50.3); symptom severity, 63.2 (vs. 76.7 and 63.3); masking index, 3.9 (vs. 3.2 and 2.8); and life impacts, 63.1 (vs. 58.4 and 49.8). **Conclusion:** The profile of patient with MCS is a middle-aged woman who is a frequent user of healthcare services, presents a long diagnostic delay and has borne a great personal, work and socioeconomic impact. The QEESI is useful for the clinical follow-up of patients, including the optimal treatment response in the case of amalgams. **Clinical Significance:** People affected by Multiple Chemical Sensitivity deserve the attention, understanding and help of health professionals and family members, to face an invisible illness for those who do not suffer from it. Support is needed and doctors must raise awareness, and make an effort to understand and address this pathology. We suggest that protocolized amalgam extraction in accredited and prepared centers can reduce symptoms and improve quality of life, generating clinical, personal, family, occupational, social and occupational benefits.

Keywords

Chemical Sensitivity, Electromagnetic Sensitivity, Mercury Poisoning, Amalgams, QEESI

1. Introduction

Multiple chemical sensitivity (MCS) is an acquired, chronic syndrome with unknown etiology and a heterogeneous clinical picture, characterized by hypersensitivity to chemical or physical substances that are typically present in the environment at concentrations not harmful to the general population [1]. Reported prevalence worldwide ranges from 0.5% to 7%, although in Spain, no studies have found prevalence higher than 0.05% [2] [3]. It predominantly affects middle-aged women, with no differences according to socioeconomic status, education, or race/ethnicity [4].

Multiple factors (genetic, toxicological, immunological, infectious, psychiatric, and neurological) seem to influence its appearance [5]-[7]. Etiological hypotheses include Rae's toxic load, the notion—so far unproven—that the disorder is a psychiatric pathology, and the theory that it arises from a dysfunction of the limbic system (activated after olfactory stimulation) [8]. The most prominent hypothesis is the central sensitivity syndrome proposed by Yumus. It encompasses different disorders because the production mechanisms are the same and therefore this person does not suffer from different pathologies but rather has a common trigger with different symptoms in different areas of the body [9].

The pathogenesis is based on the loss of tolerance to various substances, induced by small, repeated exposures or a single exposure to a high dose in any setting (occupational, environmental, accidental, or household) [10]. Once sensitization occurs, the process appears to be irreversible and progressive [11]. A myriad of substances can trigger a reaction, including cleaning products (80%); toiletries (shower gel, cosmetics, or perfumes: 75%); paints, varnishes, and solvents (50%); air fresheners, detergents, tobacco smoke, and fabric softener (20%); gasoline, tar, glue, and ink, among others (< 20%); solar exposure (29%), electromagnetic waves (10%); and sound waves or perceived seismic waves (< 6%). Some authors have postulated that the symptomatic trigger is not the substance itself, but the smell of it [12]. Other stimuli comprise different foods and metals such as mercury. A relationship between sick building syndrome [13] and occupational exposure (Gulf War veterans, exposure to pesticides) [14] has been described in the literature.

The clinical manifestations are systemic, multi-organ, recurrent, intermittent, and fluctuating in severity, and they can become disabling. The most frequent include: general (malaise, asthenia, weakness, dysthermia), gastrointestinal (nausea, vomiting, distension and abdominal pain), neurological (anxiety, distress, headache, instability, disorientation, memory loss, difficulty concentrating), respiratory (including laryngeal and nasal symptoms, sensation of nasal obstruction or irritation, rhinorrhea, itching and mucus in the throat, dry mouth, dysphonia, dysgeusia, odynophagia, sensation of glottic closure, dyspnea, dry cough), ocular (irritation and ocular dryness), and cardiovascular (palpitations, chest pain). MCS is associated with a greater prevalence of psychiatric disorders (mainly anxiety-depressive and somatization disorders). Symptoms usually appear suddenly and abate gradually when the triggering agent is identified and removed. As time passes, more and more substances trigger the symptoms, which moreover become more severe and affect more organs, finally leading the patient to drastically limit their daily activities to avoid exposure, with consequent reductions in quality of life across different domains (personal, family, work, social, etc.). According to assessments using the SF-36 questionnaire, these impacts can rival those in cancer or transplant patients [15]-[20].

The diagnosis of MCS is clinical, as the physical examination and complementary tests usually do not show abnormalities. There are no known biological markers that identify the triggering substance, except in cases of poisoning by mercury or other metals. Miller *et al.* [21] developed the Quick Environmental Exposure and Sensitivity Inventory (QEESI). This validated self-assessment questionnaire, which has been translated to Spanish, has five subscales: chemical intolerances, other intolerances, symptom severity, masking index (to assess ongoing exposures and people's awareness of them), and life impact. Each subscale, except the masking index (score 0 to 10 points), is scored from 0 to 100 points, where higher scores signify greater severity. The scale shows a sensitivity of 92% and a specificity of 95% after discarding scores of less than 20 points on the chemical intolerances scale, less than 12 points on the other intolerances scale, and less than 20 points for symptom severity [22]. In addition to being a diagnostic tool, it can be used as

a severity and prognostic criterion to evaluate temporal progression in the different subscales. The differential diagnosis includes allergic, respiratory, immunological, and psychiatric disorders.

No specific treatment for MCS exists. The only strategies to reduce symptoms are avoiding the culprit substances, based on trial and error with accidental exposure to the possible triggers; taking vitamin complexes, trace elements, and antioxidants; and leading a healthy lifestyle with moderate and individualized physical activity [23]. Exclusion diets and supplements have not been shown to be associated with clinical improvement. For inhalation exposure, the use of masks and ventilation in closed spaces (work offices, school classrooms, etc.) appear to be effective, but corticosteroids, antihistamines, and chelators are not. People with electromagnetic hypersensitivity usually move to areas far from urban centers to reduce exposure [24]. In mercury hypersensitivity secondary to dental amalgams, a potential etiological treatment can be proposed, consisting of controlled, protocolized, progressive and spaced extraction of amalgams, to be replaced by fillings that do not generate hypersensitivity. Reported clinical outcomes after amalgam removal are mixed and inconclusive [25]. Therefore, although this practice is not systematically established, dental protocols to extract the amalgams in a safe manner for the patient and the team are being worked on, since mercury gases are released in large quantities during the procedure. The extraction does not imply the elimination of the mercury already deposited in the tissues, but it is the first step to stop its accumulation.

Currently, MCS continues to be a poorly recognized and scarcely studied entity. In Spain, there are few published case series, and none analyze the evolution of the disease over time. Our main objective is to describe the sociodemographic, clinical, analytical, and treatment-related characteristics of cases diagnosed with MCS, with a special focus on mercury hypersensitivity. As secondary objectives, the sociodemographic profile and comorbidities will be compared in patients with versus without amalgams, and the disease course (as measured by the QEESI) will be compared in patients without amalgams and with amalgams before and two years after extraction.

2. Methods

2.1. Study Design and Population

This retrospective, longitudinal cohort study included consecutive patients diagnosed with MCS and treated in the Internal Medicine outpatient clinic of the University Hospital of San Juan de Alicante from 1 January 2008 to 1 January 2021. The study period considered has been necessary due to the complexity of patient recruitment, partly due to the lack of knowledge of this entity.

Inclusion criteria were: patients clinically diagnosed according to the consensus-based definition for MCS [26], aged 18 years or older, and signed informed consent. Exclusion criteria were: lost or incomplete QEESIs; QEESI score of less than 20 points on the chemical intolerances scale, less than 12 points on the other

intolerances scale, and less than 20 points on the symptom severity scale; or refusal to sign informed consent.

2.2. Data Collection and Study Variables

A data collection form was designed with two differentiated sections: the first included sociodemographic variables (age, sex), toxic habits, comorbidities, and disease-related characteristics (type of MCS, duration, sick leave, number of visits to health services prior to diagnosis). This section was completed through a clinical interview carried out either electronically or in person. In the second section, longitudinal data were collected for the self-completed QEESI questionnaires, which were administered during follow-up visits over the study period. In patients with amalgams, the QEESI was filled out at baseline, at two months after each extraction, and every six months following removal of the last fillings, in the week prior to the outpatient appointment. To assess the evolution in these patients, results of the baseline QEESI (prior to removing any amalgam) were compared with the last one completed, two years after all the amalgams had been removed. Only patients with amalgams were monitored because an active measure (protocolized removal of amalgams) was performed, vs. patients with mercury exposure who did not have amalgams.

In addition, all patients periodically underwent a general blood test prior to the visit to the outpatient clinic. Mercury levels in blood and 24-h urine were monitored only in patients with amalgams (N = 16) or a history of mercury exposure (N = 4).

2.3. Statistical Analysis

Statistical analyses were performed using the IBM SPSS 26 statistical package. Qualitative variables were described as absolute and relative frequencies and compared with the chi-squared test or Fisher's exact test, as appropriate. Quantitative variables were expressed as mean and standard deviations (SD) and compared by means of the student's t test for independent data. In patients with amalgams, mean differences (MDs) in QEESI subscales were calculated from baseline to end of follow-up (2 years after removal of all amalgams), using the student's t test for paired data. Mixed linear models were constructed with the linear and quadratic powers of time as fixed effects and the individual as random effects. Through these models, mean values for each QEESI subscale were represented over time using fixed effects. Subgroups with versus without amalgams were compared. All calculations were performed with a type I error of 5%.

2.4. Ethics

The Clinical Research Ethics Committee of the Hospital de San Juan approved the study (ref. 15/302). All patients signed informed consent prior to inclusion.

3. Results

Of the 40 patients recruited, 1 patient not covered by social security was excluded,

along with 6 with incomplete QEESI questionnaires. Thus, the final sample comprised 33 patients: 24 women (72.7%) with a mean age of 56.2 years (SD 14.4, range 20 - 80) and 9 men (27.3%) with a mean age of 59.6 years (SD 13.1, range 37 - 82).

Table 1 shows a summary of patient characteristics, both overall and by subgroups (n = 16 [48.5%] with amalgams, n = 17 [51.5%] without). None drank alcohol, and most had either never smoked (n = 21, 63%) or had quit (n = 7, 21%), on average 16 years before the study (mean cumulative consumption 15.3 pack-years, SD 6.6). The 5 (15%) smokers had a mean cumulative consumption of 20 pack-years (SD 16.8). The sample's mean body mass index (BMI) was 26.1 kg/m^2 (SD 5.9).

The most frequently reported symptoms were intense asthenia and muscle weakness (91%); nausea, abdominal discomfort, and digestive problems (87%); memory loss, insomnia, emotional susceptibility, and difficulty concentrating (84%); headaches (64%); and ocular and/or nasal irritation and itchy throat (57%). Improvements were observed in the subgroup with amalgams and after completing the extraction procedure, who reported less asthenia, headaches, nasal irritation, emotional susceptibility, abdominal discomfort, and food tolerance compared to the subgroup without amalgams (p = 0.057).

Many patients with MCS (n = 15, 45.4%) did not have comorbidities (men = 5, 33.3% versus women = 10, 66.7%). Among the rest of the sample, the most common were fibromyalgia (n = 13, 39.4%), mostly in women (n = 12, 92%, p = 0.1) and chronic fatigue syndrome (CFS) (n = 7, 21.2%, all in women, p = 0.15). Eight patients (24.2%) had hypertension (4 in the subgroup with amalgams and 4 in those without; p = 0.9). Similarly, eight patients had dyslipidemia (men = 2, 12.5% versus women = 6, 35.2%; p = 0.22). None of the patients had diabetes. Anxiety (n = 18, 54.5%) and depression (n = 13, 39.3%) were also more prevalent among the women (n = 15 [83%], p = 0.4 and n = 10 [77%], p = 0.9, respectively). The most frequent psychiatric and syndromic comorbidities in the group with amalgams (vs. without amalgams) were: fibromyalgia 37.5% (vs. 41%; p = 0.82); CFS 12.5% (vs. 29.4%; p = 0.39); anxiety, which was the most prevalent comorbidity in both groups (56.3% and 53% respectively; p = 0.84); and depression 37.5% (vs. 41.2%; p = 0.82). None of the men with amalgams presented fibromyalgia, CFS or anxiety, and only one had depression (Figure 1).

Only one (3%) patient required admission. Two (6%) deaths were recorded, one from acute myocardial infarction at home and another from severe community-acquired pneumonia.

Regarding the type of MCS, this was due to chemicals in 26 (78.8%) patients: 16 (48.5%) had dental amalgams, 4 (12.1%) had high levels of mercury in their blood due to exposure from other sources (2, paint; 1, contact with biocides, fungicides and pesticides; and 1, unknown origin), and 6 (18.2%) had hypersensitivity to chemical substances other than mercury. Moreover, 8 (24.4%) patients had electromagnetic hypersensitivity, and 22 (66.7%) had food intolerance.

Table 1. Characteristics of patients with multiple chemical sensitivity, with and without dental amalgams.

Variables			Total (N = 33)		Dental amalgams (N = 16)		No amalgams (N = 17)	
			Women	Men	Women	Men	Women	Men
Sex, n (%)			24 (72.7%)	9 (27.3%)	13 (81%)	3 (19%)	12 (70%)	5 (29%)
BMI, mean kg/m^2 (SD)			26.1 (5.9)		25.3 (5.0)		26.6 (6.6)	
Age, mean (SD) in years			56.2 (14.4)	59.6 (13.1)	56 (14.9)	54 (7.6)	54 (14.3)	62.6 (15.4)
Tobacco use	Never smoker	n (%)	21 (63%)		10 (62%)		11 (65%)	
	Ex-smoker	n (%)	7 (21%)		3 (18%)		3 (18%)	
		Pack-years, mean (SD)	15.3 (6.6)		13.4 (8)		-	
		Years since quitting, mean (SD)	16 (1.1)		18.8 (14.3)		-	
	Current smoker	n (%)	5 (15.2%)		2 (12.5%)		3 (17.6%)	
		Pack-years, mean (SD)	20 (16.8)		12.5 (11.2)		-	
Cardiovascular risk factors, n (%)		Hypertension	8 (24.2%)		4 (25.0%)		4 (23.5%)	
		Dyslipidemia	8 (24.2%)		2 (12.5%)		6 (35.2%)	
Sick leave, n (%)			11 (33.3%)		6 (37.5%)		5 (29.4%)	
Duration of sick leave in days, mean (SD)			430.6 (405.3)		327.6 (247.7)		554.2 (546.9)	
Months from symptoms onset to diagnosis, mean (SD)			120 (81.6)		121 (86)		119 (72.1)	
Health services use	Health service consulted, n (%)	Primary health care	131.2 (77.8)	86.2 (89.2)	142 (83.1)	36 (59.2)	120 (64.2)	116 (97.6)
		Secondary care	28 (84.8%)		13 (81.3%)		15 (88.2%)	
		Mental health	26 (78.8%)		12 (75.0%)		14 (82.4%)	
	N visits to health services, mean (SD)	Primary health care	15 (45.4%)		7 (43.7%)		8 (47.1%)	
			21.4 (16.6)		24.35 (17.7)		20.25 (15.4)	
			24.6 (16.4)	12.3 (14.5)	27 (17.6)	8.5 (7.8)	22 (15.1)	16.2 (17.1)
		Secondary care	9 (7.3)		10.1 (8.6)		8.7 (6.2)	
			10.9 (7.4)	3.9 (3.7)	11.25 (8.77)	3.5 (3.53)	10.45 (6)	4.8 (4.2)
		Mental health	5.6 (8.5)		3.8 (5.9)		7.6 (10.2)	
			6.3 (9.1)	3.7 (7.1)	4.4 (6.1)	0	8.36 (11.2)	6 (8.3)
Comorbidities, n (%)		Anxiety	18 (54.5%)		9 (56.2%)		9 (53%)	
			15	3	9	0	6	3
		Depression	13 (39.3%)		6 (37.5%)		7 (41.2%)	
			10	3	5	1	5	2
		Chronic fatigue syndrome	7 (21.2%)		2 (12.5)		5 (29.4%)	
			7	0	2	0	5	0
		Fibromyalgia	13 (39.4%)		6 (37.5%)		7 (41%)	
			12	1	6	0	6	1

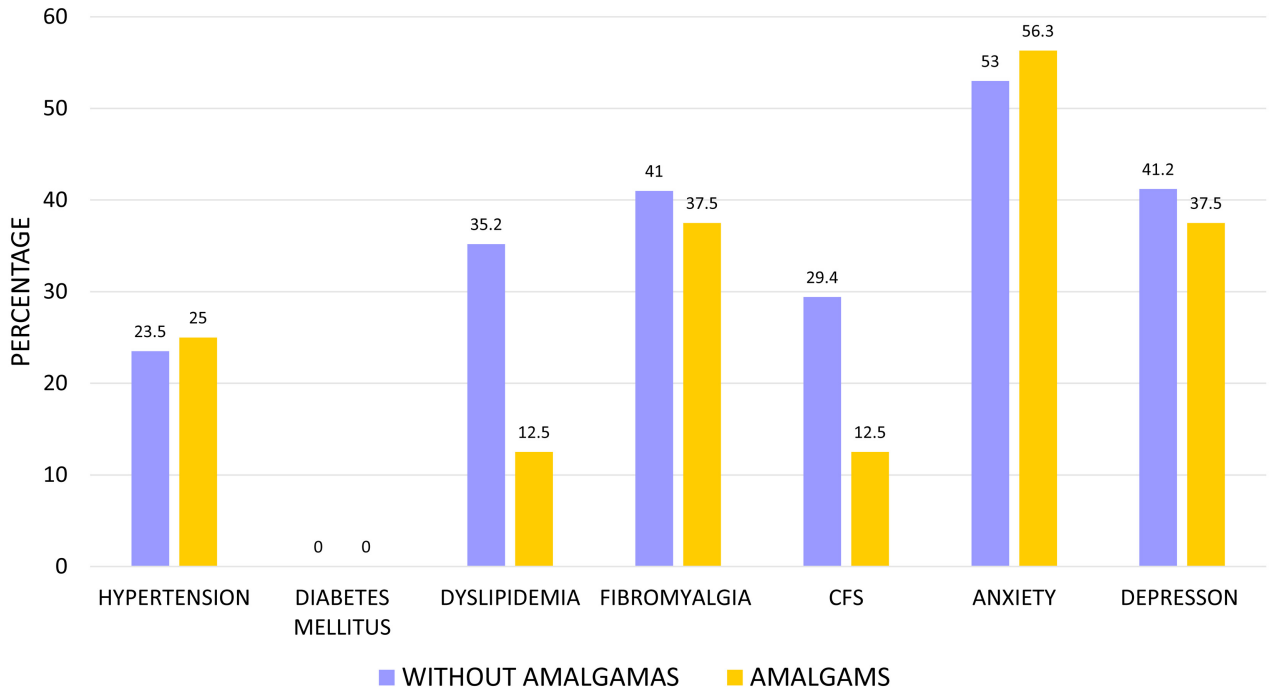

Figure 1. Comorbidities in patients with and without amalgams. CFS: chronic fatigue syndrome. There were no significant differences between the two groups ($p > 0.05$ for all comparisons).

The amalgam subgroup (13 women, 3 men) had an average of 5 fillings (range 2 - 12). There were no differences between subgroups in terms of gender, age, BMI, or tobacco use ($p = 0.8$). The 4 patients with a history of mercury exposure but without amalgams (3 women, 1 man) were included in the subgroup without amalgams.

Laboratory results showed only 3 cases of iron deficiency without anemia, in one patient with six amalgams and two without amalgams. Inflammatory parameters (erythrocyte sedimentation rate and C-reactive protein) and kidney function were normal in all patients. The amalgam group presented a progressive decrease in blood mercury levels and stable urine levels. In the four patients with mercury exposure and without amalgams, blood and urinary levels increased progressively (**Figure 2**).

The mean time from symptoms onset to diagnosis was 120 months (SD 81.6), with a marked difference between men (86.2 months, SD 89.2) and women (131.2 months, SD 77.8) ($p = 0.17$). Before diagnosis, the patients had presented to different health services: 28 (84.8%) at primary health care (PHC), 15 (45.4%) at mental health services (psychiatrist and/or psychologist), and 26 (78.8%) to other specialized units (rheumatology, allergology, gastroenterology, internal medicine, pulmonology). On average, patients visited PHC 21.4 times (SD 16.6), with women having to see their family doctor an average of 24.6 times (SD 16.4) compared to 12.3 times (SD 14.5) in men ($p = 0.09$). Mean visits to mental health services numbered 5.6 (SD 8.5): 6.3 (SD 9.1) in women and 3.7 (SD 7.1) in men ($p = 0.45$), and to other specialists, 9 (SD 7.3): 10.9 visits (SD 7.4) in women and

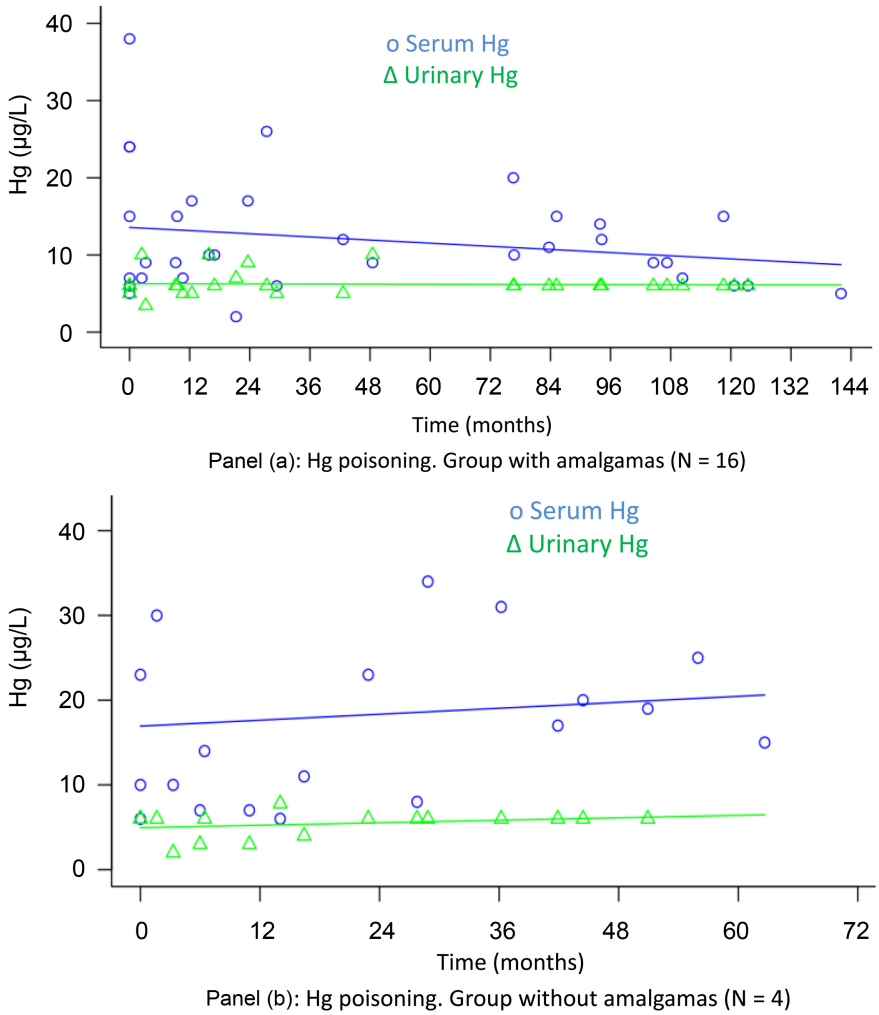

Figure 2. Mercury concentrations in blood and 24-h urine in patients (a) with amalgams and (b) with mercury exposure but without amalgams.

3.9 visits (SD 3.7) in men (p = 0.01). The number of consultations was lower in men across all specialties analyzed. Eleven (33.3%) patients—all women—were on sick leave and had been for a mean of 430.6 days (SD 405.3).

The demand for medical care was similar in patients with and without amalgams: 88% vs. 81%, respectively, had visited PHC; 82% vs. 75%, other specialist services; and 47% vs. 43.7%, mental health services. The diagnostic interval was 10 years in both subgroups; with a notable difference between sexes in the amalgam's subgroup (women: 142 months SD 83 vs. men: 36 months SD 59; p = 0.07). In the subgroup without amalgams, this interval was similar between sexes (women: 120 months SD 64 versus men: 116 months SD 97.6 in men). Six (37.5%) patients with amalgams were on sick leave, compared to 5 (25%) in the subgroup without amalgams (p = 0.48). The mean duration of sick leave in the subgroup with amalgams was 327.6 days (SD 247.7) days, versus 554.2 (SD 546.9) days in the subgroup without amalgams (p = 0.88).

A total of 114 QEESI questionnaires were collected: 82 in the group without

amalgams (mean 4.8 per patient; range 4 - 6) and 32 in the group with amalgams (one each at baseline and two years' post-extraction). The mean scores (SD) in the group without amalgams were (Table 2): 62.8 (SD 23.2) for the chemical intolerance 41 subscale; 52.7 (SD 21.7) for other intolerances; 63.2 (SD 17.6) for symptom severity; 3.9 (SD 1.6) for masking index; and 63.1 (SD 28.5) for life impact. Men obtained a higher score than women on the subscales for chemical intolerances (mean 72.9 SD 26.9 vs. 60.1 SD 21.5; p = 0.32) and life impact (67.8 SD 23.2 vs. 61.9 SD 29.7, p = 0.29). In the rest of the subscales, the results were lower in men than in women: other intolerances (44.2 SD 16.4 vs. 55.1 SD 22.4; p = 0.54); symptom severity (55.6 SD 14.3 vs. 65.3 SD 17.9; p = 0.47); and masking index (3.2 SD 1.5 vs. 4.1 SD 1.6; p = 0.87).

Table 2. Mean (SD) QEESI subscale scores, overall and by sex, in the subgroup of patients without amalgams.

	Subscale				
	Chemical intolerances	Other intolerances	Symptom severity	Masking index	Life impact
Overall (N = 33)	62.8 (23.2)	52.7 (21.7)	63.2 (17.6)	3.9 (1.6)	63.1 (28.5)
Women (N = 24)	60.1 (21.5)	55.1 (22.4)	65.3 (17.9)	4.1 (1.6)	61.9 (29.7)
Men (N = 9)	72.9 (26.9)	44.2 (16.4)	55.6 (14.2)	3.2 (1.5)	67.8 (23.2)

Over the course of the study period (Figure 3), scores increased by 7.2, 19 and 13 points in the subscales for chemical intolerances, other intolerances, and life impacts, respectively. There was an initial decrease of 3 points and a subsequent increase of 5 points for symptom severity and a decrease of 1 point in the masking index subscale.

The 16 patients with amalgams voluntarily underwent protocolized removal of their fillings until complete extraction. We analyzed the MD in QEESI scores at baseline and two years after the last amalgam was extracted (Table 3, Figure 4). For the chemical intolerance subscale, the mean score was 63.4 points at baseline versus 46.7 points at last follow-up (MD 16.7, p = 0.083); for other intolerances, 62.8 points versus 50.3 points (MD 12.5, p = 0.067); symptom severity, 76.7 points versus 63.2 points (MD 13.5, p = 0.099); masking, 3.2 points versus 2.8 points (MD 0.4, p = 0.9); and life impact, 58.4 points versus 49.8 points (MD 8.6, p = 0.072).

With regard to management, all patients adopted avoidance measures (81% dietary). Three-quarters limited their diets to organic foods, and 63% began taking vitamin supplements. Twelve percent regularly used a mask at home, at work, and on public roads (pre-pandemic). Only one patient underwent desensitization therapy, without success. All the patients with amalgams voluntarily decided to have their fillings removed. Of the eight patients with electromagnetic sensitivity, four (50%) moved house; two experienced an improvement in symptoms, while the other two saw a worsening.

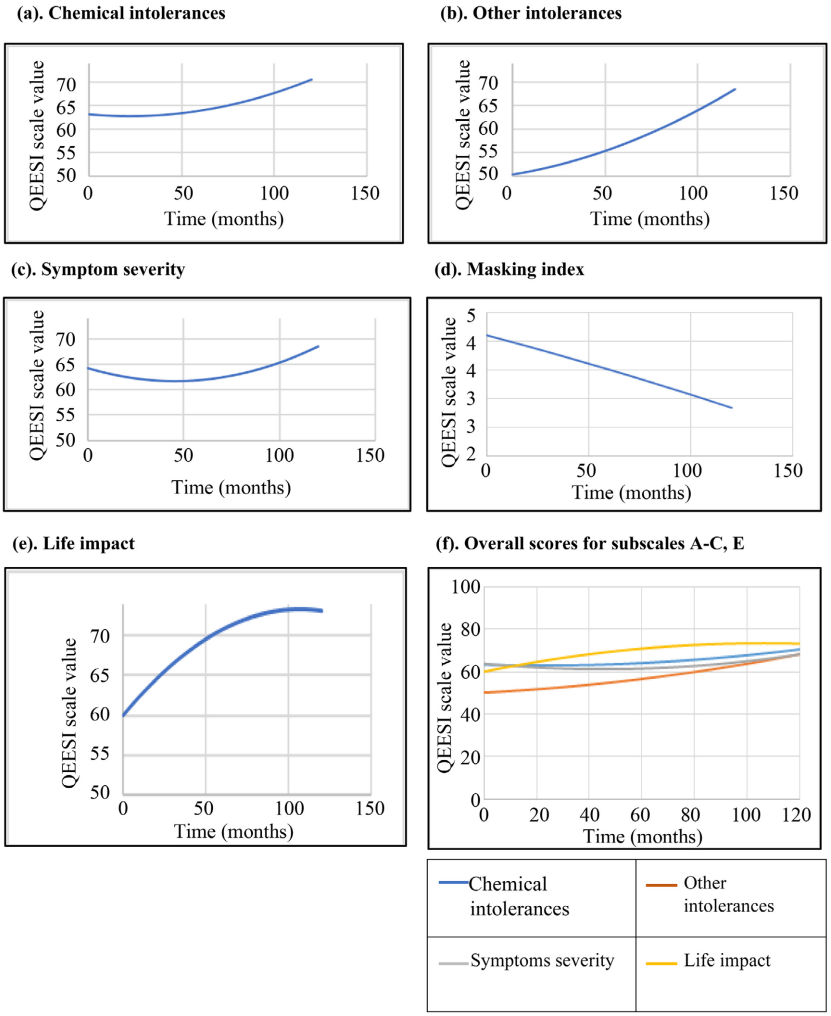

Figure 3. Temporal evolution of QEESI subscale and overall scores in subgroup without amalgams.

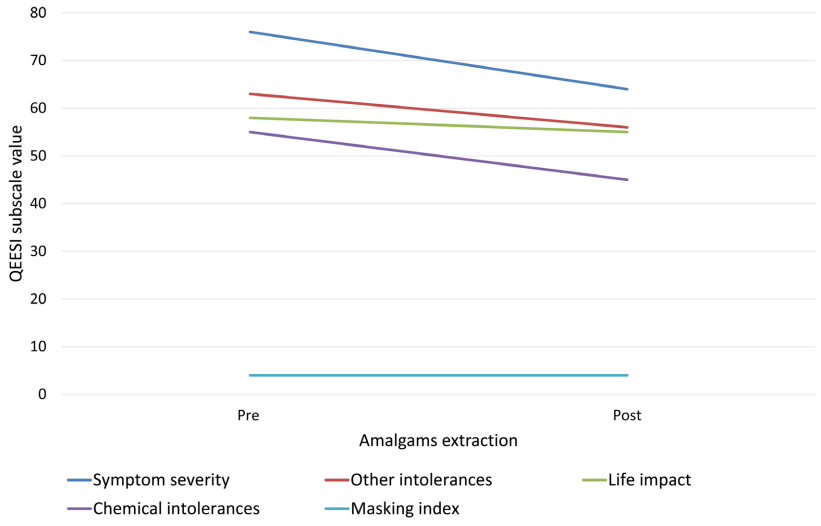

Figure 4. Evolution of QEESI subscale scores from baseline to last follow-up (2 years after extraction of last amalgam).

Table 3. Comparison of QEESI subscale results at baseline versus 2 years after extraction of the last dental amalgam (N = 16).

	Mean difference (SD)	95% CI	P value
Chemical intolerances	16.7 (16.2)	−1.9, 23.12	0.083
Other intolerances	12.5 (17.27)	−1.05, 25.51	0.067
Symptom severity	13.5 (18.4)	−2.72, 25.62	0.099
Masking index	0.4 (0.01)	−0.77, 0.77	0.97
Life impact	8.6 (11.6)	−0.90, 16.89	0.072

CI: Confidence Interval; SD: Standard Deviation.

4. Discussion

This study collected and analyzed the characteristics and disease course in patients diagnosed and treated for MCS over 13 years, in the Internal Medicine service of our hospital. The descriptive analysis covered the sociodemographic, clinical, therapeutic, and evolutionary characteristics for the overall sample and in the subgroup with dental amalgams.

Most of our patients were middle-aged women, as described in the literature with healthy lifestyles (without toxic habits) and active workforce participation. During follow-up, 33% took sick leave for a mean period of 10.12 months (with amalgams) and 18.51 months (without amalgams). Three patients (9%) lost their jobs, two (6%) resigned, and two (6%) requested temporary or permanent disability, which entailed feelings of isolation and emotional burden. Previous studies have described a prevalence of sick leave of 10%, and a rate of workforce dropout of 85% over eight years of follow-up [27].

We observed a high prevalence of anxiety-depressive disorders, fibromyalgia, and associated CFS, in keeping with other reports [28]. However, since MCS is an underdiagnosed disease, our data may be limited by the sample size, with a consequent underestimation of these comorbidities, coinciding with the variability in prevalence described in the literature (36% to 80%) [29]. The treatment and management of depression and anxiety in these patients is similar to those without MCS.

Although more than half of the patients described psychiatric symptoms (63%), less than half had attended mental health services (45%), while 84.8% and 78% attended PHC and other specialties, respectively. This low number of visits to mental health clinics could be due to different obstacles, including extended waiting lists, self-inhibition due to social stigma, or because the patient considered that the anxiety-depressive symptoms were secondary to MCS and therefore focused their efforts on resolving the root cause. This aspect has not been studied in the literature.

The number of visits to health services was lower in men in both subgroups (with/without amalgams) and for all specialties analyzed. Although the extensive odyssey that patients go through across different medical services in search of a

diagnosis has been described elsewhere, the topic has not been studied in depth or quantified. The average time elapsed between the onset of symptoms and diagnosis—120 months, or 10 years—is longer than previously described (69 months on average). This long delay may be a function of the unusual, varied, and poorly understood symptoms (both for the patient and for many doctors), combined with the unremarkable results of complementary medical tests and the skepticism and rejection they encounter among family, friends, and work colleagues ("it is a sickness of suffering, not dying", as patients themselves usually conclude). The difference of more than 100 months in diagnosis between women and men is notable, not described in the literature, and could be attributed to the profile of the patients, the non-specific and subjective clinical manifestations, and the associated comorbidities. In this scenario, the attending physician may suspect a psychiatric, rheumatic, or allergic disorder rather than MCS. As it is a little known and poorly recognized disease, the true prevalence of MCS is very likely to be underreported, and few professionals would be familiar enough with the condition to consider it in the differential diagnosis. The consequent diagnostic delay results in an inefficient use of healthcare resources, unnecessary visits, and a feeling of frustration among patients due to the lack of care, causing worsening satisfaction and distrust in the system.

The most frequent psychiatric and syndromic comorbidities observed in both subgroups were anxiety, fibromyalgia, and depression. CFS was more common in patients without amalgams. The prevalence of anxiety-depressive disorders observed in patients with amalgams is consistent with other studies (40% to 80%). We are not aware of any studies that compare MCS patients with and without amalgams.

The evolution of QEESI scores in the subgroup without amalgams (including the 4 patients with mercury exposure) confirms the progressive nature of the disease (subscales for chemical and other intolerances). These data support the theory of central sensitivity. Symptom severity also increases despite avoidant behaviors, which may be due to the progressive involvement of more organ systems. The subscale showing the greatest difference over time is that of life impacts. This finding reflects the limitations imposed by the disease and the resulting changes that can be disabling. Comorbidities make recovery difficult, in keeping with the irreversible and progressive evolution of the disease. On the masking index subscale, there is a small decrease (1 point), possibly because after the long diagnostic delay, the patients would have already identified some disruptors that affect them and would have taken measures to eliminate or avoid them in their daily life – prior to performing the baseline QEESI.

In general, the only treatment option for people with MCS is to avoid the identified triggers. In all cases analyzed, patients followed this course of action. Despite their avoidance measures, the scores on the severity subscale do not show improvements in symptoms or self-perception of the disease, as described elsewhere. With the aim of improving tolerance to disruptors, some authors have explored

systemic desensitization techniques using cognitive-behavioral therapy. Only one patient in our series used this technique, without clinical improvement.

Regarding mercury exposure, the series studied show the most relevant source of mercury hypersensitivity is dental amalgams. Mercury is considered a global pollutant; key exposure routes include contact with paints and aerosols without the proper use of protective masks (in professional painters, for example) and more commonly through amalgams. Dental fillings for cavities have long been made with liquid mercury, silver, and copper, but in recent years the use of this alloy has decreased dramatically due to evidence demonstrating the release of mercury vapors and inorganic mercury compounds. These are absorbed into the body through the respiratory and digestive systems, causing an increased concentration in blood and urine, which in turn generate immunological, neurological, or other problems, including the symptoms of MCS and its comorbidities. To calculate the total mercury load, it is useful to measure its concentrations in plasma and urine. However, there is no correlation between these levels and MCS symptoms from amalgams. In general, mercury levels are under 5 pg/mL in urine and 15 pg/mL in blood. Although these are relatively low concentrations, they can accumulate over time, preventing optimal cell function.

The 16 patients with amalgams underwent protocolized extraction. QEESI scores at baseline and two years post-extraction showed a decreasing trend on all five subscales, also coinciding with the progressive decrease in blood mercury levels and little change in 24-h urine. On the other hand, in the four patients exposed to mercury from sources other than amalgams, their blood mercury levels actually rose over time, probably due to the mobilization of organic deposits. This finding coincides with the progressive worsening of symptoms and self-reported scores on the QEESI. Although the statistical analysis was underpowered due to the small sample size, the outcomes were clinically significant in the amalgam subgroup. Our results suggest that the extraction of amalgams can reduce symptoms and improve quality of life, generating clinical benefits and leading to a reduction in sick leave. Thus, we agree with previous recommendations on performing the protocolized extraction in this subgroup of patients [18] [30].

Limitations of our study include the retrospective observational design, the small sample size, probably due to the dispersed demand for specialized consultations and the delay in referral to Internal Medicine, factors that would affect patient recruitment and limit the statistical power of the analyses. It would be beneficial to include objective measures of MCS symptoms, such as neurocognitive testing or physiological assessments, in addition to the QEESI; as well as to collect detailed information on potential confounders, including environmental exposures, lifestyle, and other medical conditions, to control for their influence on the analysis.

On the other hand, strengths include the collection and tabulation of all data by a single researcher, minimizing heterogeneity in data entry and validation. In addition, the included patients come from real-world clinical practice, and the study

population mainly covers the catchment area of the Hospital de San Juan, so the conclusions could potentially be applicable to the population, although we propose carrying out of prospective and multicenter studies that validate our results.

5. Conclusion

The profile of the patient with MCS is predominantly a middle-aged woman of working age, with mainly psychosocial comorbidities and fibromyalgia. Patients are frequent users of healthcare services who often seek help for years before being diagnosed with MCS and bear great personal, work, social and economic impacts from the disease. The QEESI questionnaire is useful for the clinical follow-up of patients, including to evaluate the optimal treatment response in the case of amalgam carriers.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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