



# A case report of idiopathic environmental intolerance: A controversial and current issue

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## Abstract

In this case of idiopathic environmental intolerance, a little known disease characterized by many symptoms of irritation due to exposure to several toxic compounds, genetic analysis could be helpful in case of differential diagnosis issue.

## KEYWORDS

genetic liability, idiopathic environmental intolerance, multiple chemical sensitivity, toxic compounds

## 1 | BACKGROUND

Idiopathic environmental intolerance also known as multiple chemical sensitivity is a little known disease characterized by many symptoms of irritation due to exposure to several toxic compounds. In this unconventional case, genetic analysis could support diagnosis, highlighting genetic liability and allowing to understand pathogenic mechanisms.

The World Health Organization believes that future expected health effects due to climate change will be among the most relevant health issues to be addressed in the coming decades.<sup>1</sup> Consequences will be relevant in the most fragile groups of the population, such as the children, the elderly, the patients suffering from chronic pulmonary disease.<sup>2</sup> Among these, a particular and less known class of frail subjects is that of patients suffering from idiopathic environmental intolerance (IEI).

In 1996 WHO workshop stated that medically unexplained conditions attributed to diverse environmental factors should be labeled under the same term, IEI due to their similar features.<sup>3-5</sup> Such conditions include multiple chemical sensitivity (MCS), hypersensitivity to electromagnetic fields, and sick building syndrome.

IEI also known as MCS is a heterogeneous syndromic condition attributed to exposure to trace levels of environmental agents such as indoor air environments and electromagnetic fields or chemicals at nontoxic concentrations<sup>6-8</sup> and characterized by intolerance to multiple chemical substances (xenobiotics) even at low doses. It is a chronic acquired disorder characterized by nonspecific symptoms in multiple organ systems ranging from annoyance to severe disability<sup>8</sup>: Patients show nonspecific symptoms (asthmatic-like, skin irritation, dermatitis, migraine, dysuria, dyspepsia, symptoms of supposed sensitization to food, persistent arthromial pain, vertigo, vestibular impairment).<sup>9-12</sup> In 80% of patients the predominant symptoms are asthenia, arthromial pain, dyspepsia, coriza, eructation, chest pain, insomnia.<sup>13</sup> IEI/MCS is a widespread public health problem<sup>14</sup> currently considered a special case of chemical intolerance (CI), or a tendency to develop nonspecific symptoms involving multiple systems (eg, nervous, gastrointestinal, ocular) in response to exposure to some specific chemicals. The prevalence of the CI is 33% in the general population, while the MCS has a prevalence between 0.5% and 6%.<sup>15</sup> IEI are reported significantly more often by women than men.<sup>5,8</sup>

The name and diagnostic criteria are still under debate even now so to date, the exact nosological classification of IEI/MCS is unclear. A number of hypotheses concerning its

etiology and pathogenesis have been proposed, including impairments of neurological, immunological, and psychological systems. Due to the nonspecificity of the symptomatology and considering that no instrumental or laboratory tests are decisive in the diagnosis of the pathology, the greatest weight in the diagnostic procedure is held by the anamnesis and clinical history collected also with QEES (Quick Environmental Exposure and Sensitivity Inventory).<sup>16,17</sup> According to Cullen's criteria (1987),<sup>18</sup> no functional test can explain the symptoms of IEI/MCS and therefore the diagnosis is made exclusively through the finding of a temporal and cause-effect relationship between chemical exposure and onset of symptoms. More recently, several authors tried to find tests or diagnostic markers that would help the diagnosis in order to avoid an overestimation of MCS cases due to condition that could invalidate the correct nosological classification, for example, anxiety-depressive state is very frequent in such patients).<sup>19</sup>

Among these, Azuma et al<sup>20</sup>, showed alterations in cerebral flow in MCS patients after exposure to particularly unpleasant compounds. The same author suggested also that inherent physical constitution and childhood housing environment are associated with a risk of acquiring chemical intolerance.<sup>14</sup> Others have instead shown peculiar genetic polymorphisms that can explain the symptomatology. In this regard, although in literature it is reported that 26 genes are implicated in the pathogenesis of MCS,<sup>21</sup> but only a few of these are important.<sup>22</sup> This group includes mutations of the catalase coding gene (CAT C262T homozygosity polymorphism) and of the gene encoding glutathione transferase (polymorphism with a null genotype of the GSTT1 gene and heterozygosity polymorphism of the GSTP1 A313G gene) that seem to increase cellular oxidative stress after exposure to certain xenobiotics<sup>23-25</sup> and to facilitate the onset of bronchial hyperactivity and asthmatic-like symptoms in patients with MCS.<sup>26,27</sup> On the other hand, particular polymorphisms of the CYP2D6 gene give the carrier a slow metaboliser phenotype, which leads to increased blood concentrations of the same xenobiotics and the consequent oxidative stress.<sup>28</sup> It is known, moreover, that the null genotype of the GSTT1 gene predisposes to the accumulation of DNA-hippuric acid adducts<sup>29</sup>: This compound is a metabolite of many chemicals with an aromatic structure, including some disinfectants, such as benzyl benzoate and the benzalkonium chloride, as well as the more known benzene and toluene<sup>30</sup> and its accumulation is indicative of a previous exposure to such toxicants.<sup>31</sup>

Patients suffering from MCS and carriers of these genetic anomalies are therefore strongly exposed to the development of phlogistic reactions of various organs and systems, in particular the ocular mucosae, oronasal, and tracheal.<sup>32-34</sup> In hospitals, there are several xenobiotics that induce this symptomatology. Among the main ones we mention formaldehyde,<sup>35</sup> the surfactant compounds such as sodium-lauryl-sulfate-containing soaps and alkyl-benzenesulfonic

acids, benzalkonium chloride, sodium hypochlorite, quaternary ammonium derivatives, and polyglycosidic ammonium derivatives.

Equally, important are the aromatic and aliphatic hydrocarbons, esters, ethers and resins, or paints.

As regards the environmental pollution, the effects on human health, both direct and allergic, have been extensively studied,<sup>36-41</sup> on the contrary little is still known about health effects due to exposure to low doses of indoor chemical substances (xenobiotics) in predisposed subjects.

Healthcare workers, especially if they have an unfavorable genetic condition, are therefore exposed to both multiple sensitizations to these chemicals and to multiple exacerbations of the syndrome.

## 2 | CASE PRESENTATION

The 42-year-old GVS worker, born at the end with eutocical birth, was a never smoker professional nurse and has always served in the pediatric department since 2004. The remote pathological history is silent except for a displaced tibia fracture in 2010, resolved with slight permanent outcomes. The worker had always been in good health until 2014. In this year, she was subjected to a medical examination for health surveillance in accordance with Italian legislation. She reports that she has begun to experience frequent episodes of dizziness, headaches, nasal, and oropharyngeal burning in the last two years, with an irritated cough and sometimes dysphonia after exposure to some medical products containing sodium hypochlorite and benzalkonium chloride during work shift. Because of this symptomatology, she went several times to the emergency room of her hospital where a rhinofibrolaryngoscopy was performed which revealed diffuse hyperemia of the whole upper tract up to the posterior third of the vocal cords. In the suspicion of gastroesophageal reflux disease, the worker was hospitalized and subjected to esophagogastroduodenoscopy. The endoscopic examination was completely negative and the contextual biopsies taken from the antral and fundic gastric mucosa were negative for *Helicobacter pylori*. In this first hospitalization she was also subjected to pneumological, psychiatric and allergological counseling, all of which gave negative results. The patient reports that even during the subsequent two admissions to hospital she underwent otorhinolaryngology counseling, which confirmed the findings already highlighted in the first consultation. The diagnosis of discharge of the three accesses (made from August to September 2014) was acute laryngeal-tracheitis. On the basis of the acquired data, a new dermatological and allergological consultation was requested which recommends performing epicutaneous tests with the compounds present in the medical products considered responsible for the symptoms, which however

**TABLE 1** Results of genetic tests

Gene	Genotype (Result)	Possible genotypes
GSTP1 A313G	A/G	Homozygous A/A Heterozygous A/G Homozygous G/G
GSTM1	NORMAL	Normal Null
GSTT1	NULL*	Normal Null
SOD2 Ex2 + 24T>C rs4880	C/T	Homozygous T/T Heterozygous T/V Homozygous V/V (V = G,C oA)
CAT C262T	T/T*	HOMOZYGOUS C/C HETEROZIGOUS T/C HOMOZYGOUS T/T (the T allele is hypofunctional and reduces oxidative damage)
OGG1 C315G	C/G	Homozygous C/C Eterozigot C/G Homozygous G/G (the G allele is hypofunctional and reduces oxidative damage)
CYP 2D6	'4 – '10 * (Slow metabolizer phenotype)	'1- Wild Type- ACT. Normal '2- 2850 C-T- ACT. Normal '3- 2549delA- ACT. Null '3B- 1749A>G- Act. Null 2549delA -ACT. Null '4- 1846G>A- ACT. Null '5- Gene deletion- ACT. Null '6- 1707delT- ACT. Null '7- 2935A>C- ACT. Null '8- 1758G>T- ACT. Null '9- 2613-2615delAGA- ACT. Decreased '10- 100C>T- ACT. Decreased '11- 883G>C- ACT. Null '12- 124G>A- ACT. Null '14- 1758G>A- ACT. Null '17- 1023C>T -ACT. Decreased 2850C>T -ACT. Decreased '20- 1973insG -ACT. Null '21- 2573insC -ACT. Null '24- 2853A>C -ACT. Null '38 -2587-2590delGACT -ACT. Null '44- 2950G>C -ACT. Null 'XN- Gene amplification
CYP2CP'2 C430T	C/C	Homozygous C/C Heterozygous T/C Homozygous T/T (the T allele is hypofunctional and reduces oxidative damage)
CYP2C9'3 A1075C	A/A	Homozygous A/A Heterozygous A/C Homozygous C/C (the C allele is hypofunctional and reduces oxidative damage)

(Continues)

TABLE 1 (Continued)

Gene	Genotype (Result)	Possible genotypes
CYP3A4'1B392	A/A	Homozygous A/A Heterozygous A/G Homozygous G/G (the G allele is hypofunctional and reduces oxidative damage)
CYP3A5'36986	G/G*	Homozygous a/a Heterozygous A/G Homozygous G/G (the G allele is hypofunctional and reduces oxidative damage)
CYP1A2 C163'1F	A/A*	Homozygous A/A Heterozygous A/C Homozygous C/C (the A allele is hypofunctional and reduces oxidative damage)
CYP1A2 G3860'1C	G/G	Homozygous A/A Heterozygous A/G Homozygous G/G (the A allele is hypofunctional and reduces oxidative damage)
CYP2C19	'1/'1 (Normal phenotype)	'1 Wild type- ACT. Normal '2 (G19154A)- ACT. Null '3 (G17948A)- ACT. Null '4 (A1G)- ACT. Null '5 (C90033T)- ACT. Null '7 (T19294A)- ACT. Null '10 (C1953T)-ACT. Decreased '17 (C606T)-ACT. Null
PON1 A575G	A/G	Homozygous A/A Heterozygous A/G Homozygous G/G (the G allele is hypofunctional and reduces oxidative damage)
PON1 C-108T	C/T	Homozygous C/C Heterozygous T/C Homozygous T/T (the T allele is hypofunctional and reduces oxidative damage)
MPO G463A	A/G	Homozygous A/A Heterozygous A/G Homozygous G/G (the G allele is hypofunctional and reduces oxidative damage)
Enos Asp298Glu	G/T	Homozygous G/G Heterozygous T/G Homozygous T/T (the T allele is hypofunctional and reduces oxidative damage)

Note: Reader can note the five untoward polymorphisms (marked with \*) leading to oxidative phenotype and promoting MCS onset.

gave a negative result. On the basis of the negativity of all the haematochemical and instrumental tests performed, the presence of a hypersensitivity to different xenobiotics was suspected, such as MCS. In order to obtain a more objective diagnosis not only based on the clinical history reported by the employee, the female worker was advised to carry out targeted genetic analysis at an external laboratory medicine service. This exam is necessary to study the genes coding for the glutathione transferase (GSTP1, GSTM1, GSTT1), superoxide dismutase 2 (SOD2), catalase (CAT),

gene products with antioxidant activity (OGG1, PON1, MPO, eNOS), as well as to analyze the polymorphisms of the CYP2D6 gene and of other isoforms of the cytochrome p450 complex such as CYP2C9, CYP2C19, CYP3A5, CYP3A4, and CYP1A2. These exams showed a genotype with more polymorphisms typical of MCS against different loci, as reported in Table 1. At the same time, the presence of DNA-Hippuric acid adducts on the NAP2 gene was studied, which resulted to be equal to 8 ng/mL, suggestive of an important exposure to aromatic compounds precursors of

hippuric acid, such as benzalkonium and benzyl benzoate. On the basis of the medical history and the genetic tests, a judgment of unsuitability for the specific job was formulated and the worker was subsequently assigned to a new job at the administrative offices of the same hospital. In 2016, the employee is again subjected to a visit and reports the re-examination of the same symptoms in the performance of the new job. In particular, she reports that exposure to common volatile compounds, such as perfumes and deodorants, used by the users she came into contact with in her new job, re-exacerbated the symptoms. The severity of the symptoms makes it difficult even to carry out the normal activities of daily life. On the basis of the new anamnestic data reported and the medical documentation, a different judgment of suitability for the new administrative task was formulated with the following limitation: "must not come into contact with the user." Furthermore, in order to minimize the re-exacerbations of the MCS, the worker is given the possibility of restricted access to the workplace through a secondary entrance with the exclusive use of the neighboring toilets. Following the formulation of this judgment, the worker was periodically re-evaluated for over two and a half years: In the last periodic medical examination, December 2018, the employee reports good clinical compensation with almost complete remission of the respiratory symptoms and reports that she feels able to carry out her work successfully.

### 3 | DISCUSSION AND CONCLUSION

IEI/MCS is a widespread disease that has become a global public health concern<sup>42</sup> for example due to the growing use of cell phones,<sup>43-45</sup> and to date is a disorder of unknown etiology with no effective treatment.<sup>5,46</sup>

Although still under-diagnosed, which is thought to be caused by a gene imbalance involving multiple loci with antioxidant activity and consequent alteration of the neuro-immune network,<sup>47</sup> and as suggested by Hetherington<sup>6</sup> could be useful a genome-wide screening of IEI patients to elucidate genotypic features of the condition. Because of the nonspecificity of the symptoms and the lack of routine tests that can be used for the diagnosis, symptoms are frequently correlated with psychiatric or gastroenterological problems. For this reason, it would be useful to request a targeted specialist consultation to avoid classifying these disorders in a wrong nosological category. In this case, several genetic anomalies have favored an amplification of the sensitization to the xenobiotics to which the worker was exposed. Similar but not conclusive results were previously reported in studies that have investigated genotype in patients with IEI/MCS.<sup>24,48-54</sup>

Various mutations of antioxidant genes (GST, CAT, OGG1) and the slow CYP 2D6 phenotype have favored the maintenance

of high blood and tissue levels of aromatic compounds, as evidenced by the notable presence of DNA-Hippuric acid adducts on the gene NAP2, and the triggering of inflammatory responses by inhalation or contact with such agents. With regard to the latter, high concentrations of such metabolite precursors such as benzalkonium or benzyl benzoate have been associated with death from acute asthma attack.<sup>55</sup> This necessitates the removal from the workplace of workers with unfavorable toxicokinetics for these compounds. In the hospital, it is likely that this harmful potential is amplified by other commonly used volatile compounds, capable of causing dyspnea, chest constriction, bronchial hyperactivity with obstructive abnormalities of the spirometric tracing, such as sodium hypochlorite. The toxic action of this medical product in the present case was probably favored by a reduced activity of genes with antioxidant function, such as catalase and glutathione transferase.<sup>56-58</sup> Finally, the present case clearly shows how affected workers sensitize themselves to increasingly more harmless compounds over time. This mechanism, typical of MCS, indicates a starting chemical exposure that, due to a genetic predisposition, leads to the extension of the spectrum of compounds toward which irritating reactions are triggered y.<sup>59,60</sup> This makes the identification of the first link in this chain crucial in the future, in order to interrupt this pathogenetic process through the early removal of affected workers.

### CONFLICT OF INTEREST

None declared.

### AUTHOR CONTRIBUTIONS

MQ, AC, LDM: wrote the manuscript; LV, DC: revised it; ESSC, FM, MFG: involved in data acquisition; DC: involved in supervision; LV: involved in project administration. All authors were involved in the management of this patient. All authors read and approved the final manuscript.

### ETHICAL APPROVAL

Ethical approval is not necessary because all the medical and instrumental examinations were performed according to the Italian laws concerning the protection of workers exposed to occupational risks (D. Lgs. 81/2008).

### PATIENT CONSENT

Informed and written consent was obtained from the participant. The patient was informed that data from the research protocol would be treated in an anonymous way, with scientific methods and for scientific purposes in accordance with the principles of the Helsinki Declaration.

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