

# Idiopathic environmental intolerance: A comprehensive and up-to-date review of the literature

Álvaro Frías<sup>1,2\*</sup>

<sup>1</sup>FPCEE Blanquerna, University of Ramon-Llull, Barcelona, Spain, <sup>2</sup>Adult Outpatient Mental Health Center, Hospital of Mataró, Mataró, Spain.

## ABSTRACT

The objective was to provide a comprehensive and up-to-date review comprising the main findings on idiopathic environmental intolerance (IEI). Based on these results, we expect to shed some light on the mechanisms potentially involved in this pathology as well as its nosological location. A database search was performed from 1985 to August 2014. Overall, 130 studies fulfilled the inclusion criteria. Women are at high risk for IEI. Subjects with IEI exhibit higher rates of internalizing disorders (especially somatoform disorders) as well as neurotic traits. IEI is not associated with a consistent pattern of neurocognitive deficits. IEI may be triggered by chemical exposure in some vulnerable subjects. IEI subjects display higher concerns regarding chemical environmental threats and pay more attention to related stimuli. Classical conditioning as well as sensitization processes may explain generalized reactions to several chemical stimuli. Cultural modeling may play a role in the phenomenology of IEI. IEI subjects are not more sensitive to chemical substances but are more easily disgusted and display increased activation of anterior cingulate cortex during olfactory stimulation. Some genetic polymorphisms may confer greater susceptibility for IEI. There is no consistent evidence concerning toxicological findings involved in IEI. Higher impairment among IEI subjects is mainly associated with phobic avoidance of context stimuli. Evidence-based treatments are limited and are focused on reducing dysfunctionality and distress rather than cognitive distortions. Findings support a biopsychosocial approach to IEI. Data also suggest that IEI may be conceptualized as a somatoform disorder rather than an anxiety or psychotic disorder.

**Key words:** idiopathic environmental disorder, personality, genetic polymorphism, cognitive distortions, somatoform disorder.

\*Corresponding author. E-mail: afrias@csgm.cat

## INTRODUCTION

Idiopathic environmental intolerance (IEI), formerly known as multiple chemical sensitivity (MCS), is a poorly understood chronic and polysymptomatic condition [1]. Patients suffering from IEI report health symptoms, referable to multiple organ systems, which are triggered by harmless odors and/or electromagnetic fields and therefore are medically unexplainable [2]. Some patients diagnosed with sick building syndrome may also be included within this broad category [3]. Diagnosis of IEI ranges from 0.2% to 20.3% of the population, depending on the sample recruited and the diagnostic criteria used [4–10].

The most frequent complaints attributed to IEI are headache, memory loss, fatigue, sore throat, sleep disturbances, trouble thinking, shortness of breath, back pain, mood changes, muscle aches, and nausea [8,11]. Hence, exposure-related symptoms associated with IEI can be divided into non-specific complaints of the central nervous system (main characteristics) and functional disturbances in other organ systems (optional complaints) [12].

There is an overtly important discussion regarding the etiopathogenia and nosological status of this syndrome. Many members of the medical community are reluctant

to accept either the pathophysiologic or the psychological mechanisms involved in this pathology [13–18]. Moreover, IEI is often misdiagnosed as asthma or an allergic condition which means that patients are frequently referred to respiratory and allergy specialists. Misdiagnosis can lead to many futile medical investigations [19,20].

## OBJECTIVE AND METHOD

This manuscript aims at providing a comprehensive and up-to-date review comprising the main findings on IEI. Based on these results, we expect to shed some light on the potential mechanisms involved in this pathology as well as its nosological location.

## Search Strategy

A literature search was carried out through PsycINFO and PubMed databases from 1985 to August 2014. The terms employed include indexing terms (e.g., MeSH) and free texts: [(multiple chemical sensitivity OR idiopathic environmental intolerance) AND (prevalence OR etiopathogenia OR diagnosis OR treatment)].

## Selection Criteria

Inclusion criteria included adult people either clinically diagnosed with IEI/MCS or subjects with high scores (analogue patients) on chemical sensitivity questionnaires [21–23]. Thus, 130 manuscripts fulfilled the inclusion criteria. Three of them were overall revisions and the other seven were partial revisions. The remainder were original papers.

## Data Extraction

Results from these manuscripts were arranged according to the following categories: (i) sociodemographic characteristics, (ii) comorbid mental disorders, (iii) personality traits, (iv) neurocognitive profile, (v) triggering events, (vi) non-biological processes (both cognitive and behavioral), (vii) biological findings (somatosensorial, genetic, neurofunctional, neurophysiological, and toxicological/neurochemical/neuroendocrine), (viii) dysfunctionality, and (ix) treatment (psychological, psychiatric, and others).

## RESULTS

### Sociodemographic Characteristics of IEI Subjects

Regarding gender, most studies have shown greater percentage of women in IEI samples [4,6,24–26]. The odds ratios range from 1.63 to 3.0 [27,28].

Concerning age at onset, research agrees that IEI onset occurs most in middle-aged subjects, on average after the age of 30 years [4,26,29].

### Comorbid Mental Disorders in IEI Subjects

Prospective follow-up studies (up to 9 years) indicate that three-quarters of IEI subjects met DSM-IV criteria for a lifetime mood disorders and half of the subjects met criteria either for anxiety disorders or somatoform disorder. In addition, at least one-third of IEI people are also diagnosed with a personality disorder [11,30,31]. Conversely, IEI has not been consistently associated with lifetime substance disorders or psychotic disorders [29,32]. Some longitudinal assessment reveals that these mental disorders tend to appear before IEI complaints [6,33].

Moreover, cross-sectional studies have also found higher rates of somatoform, affective, and/or anxiety disorders in IEI subjects compared to healthy controls and/or asthmatic patients [9,34–36]. Particularly, some studies evidence a higher relative prevalence of somatoform disorders (up to 50%), mainly for chronic fatigue and/or fibromyalgia [26,37–39].

### Personality Traits in IEI Subjects

Several studies have found that experienced symptoms caused by supposed electromagnetic fields exposure are explained by somatosensory amplification (tendency to experience a somatic sensation as noxious and disturbing) [40,41]. Furthermore, patients with IEI score significantly

higher in anxiety sensitivity, trait anxiety, and harm avoidance compared to healthy controls [37,42–44]. Additionally, somatic attributions among IEI patients are mediated by anxiety traits [45].

Other studies indicate that IEI symptoms are partly associated with alexithymia [46], whereas absorption (openness to unusual experiences and suggestions) has yielded mixed results [40,47].

### Neurocognitive Profile of IEI Subjects

Studies aimed at determining the neuropsychological profile of IEI subjects have not yielded significant differences between IEI subjects and healthy controls in verbal memory, executive functions, processing speed, and psychomotor functioning [48–53]. Strikingly, most of these studies show poorer visual memory among IEI patients compared to healthy controls [48,51,52]. Overall, these results partly contradict subjective complaints of IEI subjects about decreased concentration and verbal memory loss and suggest other possible explanations (e.g., modulating role of depressed mood) rather than potential alterations in the central nervous system.

### Role of Triggering Events in IEI

There is no clear evidence regarding the role of prior stressful life events at the onset of IEI [54–57].

Conversely, comparative prevalence rates from some IEI cohorts (e.g., Gulf War military personnel) as well as retrospective data from the whole IEI population tend to indicate that exposure to chemical agents may trigger IEI symptoms [5,7,26,32,58]. These findings raise the question whether IEI pathology may ultimately represent an immuno-allergological response.

### Non-biological Processes Involved in IEI

#### *Cognitive processes involved in IEI*

Neurocognitive and neurophysiology tasks show that IEI patients display higher attention or hypervigilance to unpleasant bodily sensations than healthy controls [59,60]. Moreover, IEI patients remember these triggering sensations better [61]. Furthermore, IEI subjects exhibit more prominent cognitions of environmental threat than healthy controls [45,62]. Overall, these cognitive processes are associated with somatic attributions in IEI patients [62].

#### *Behavioral processes involved in IEI*

From a social learning approach, some studies point out the role of culture and media in psychosomatic disorders in general and IEI specifically [63,64]. With respect to experimental research, subjects who had previously watched films/warnings about the adverse effects of supposedly hazardous substances experienced increased health-related worries and more symptoms, and attributed them to sham/neutral exposure [65,66].

Likewise, prevalence data for IEI tend to be higher in the American population compared to European samples [4,7,8], suggesting a potential greater role of the media in the United States.

Regarding classical conditioning processes involved in acquisition of odor fear, laboratory studies with healthy subjects show successful fear conditioning irrespective of hedonic character [67–71]. These results may explain the generalization effect to previously neutral odors in IEI subjects. Some studies also underline that this generalization effect is mediated by the negative affectivity of the participants [72].

Concerning operant conditioning processes, it has been suggested that IEI subjects tend to deal with anxiety by avoiding those threatening stimuli (negative reinforcement). Ultimately, patients who suffer from IEI usually exhibit phobic avoidance along with prominent cognitions of environmental threat [73].

## Biological Findings in IEI

### *Somatosensory findings in IEI*

Research on chemosensory function has been carried out to determine whether IEI subjects have a heightened sensitivity to environmental odors and magnetic fields as evaluated by objective psychophysical and electrophysiological measures.

Concerning electrosensibility tasks, individuals with IEI display either higher or similar detection performance compared to healthy controls [74,75]. Regarding olfactometric investigations, IEI patients have not manifested lower threshold sensitivity than healthy controls [76–79], with the exception of a single study [80]. However, the former group tends to feel more unpleasant to a larger number of odors than the controls [76,78,79,81–83]. These results point toward alterations in the cognitive-affective processing of olfactory information as a major characteristic of IEI [84].

### *Genetic findings in IEI subjects*

Genetic research provides remarkable data concerning potential gene candidates involved in IEI pathology [85]. Several studies show that NAT2 (arylamine N-acetyltransferase 2), GSTM1 (glutathione S-transferase Mu 1), CYP (cytochrome P450), and GSTT1 (glutathione S-transferase theta 1) polymorphisms are associated with the severity of chemical sensitivity [86–90].

### *Neurofunctional findings in IEI subjects*

Functional neuroimaging studies during olfactory stimulation reveal that IEI subjects display the increased activation of either the anterior cingulate cortex or the prefrontal cortex compared to healthy controls [91,92].

Furthermore, studies focused on basal activation as ascertained by positron emission tomography (PET) show no significant differences between IEI patients and healthy controls [50,93]. Moreover, one study using single photon emission computed tomography (SPECT) underscores

hypoperfusion in small cortical areas of the right parietal and both temporal and fronto-orbital lobes in IEI subjects compared to healthy controls [94].

### *Neurophysiological findings in IEI subjects*

A remarkable part of neurophysiological studies carried out in IEI subjects have tested whether time-dependent sensitization may underlie this pathology. Unlike the habituation process, sensitization would explain the progressive increase in a given response (e.g., psychosomatic reaction) by the passage of time between the initial stimulus (e.g., low level of environmental substance) and subsequent intermittent exposures to related stimuli (e.g., other environmental substances). Limbic and mesolimbic brain regions are among the most sensitizable to repeated, intermittent environmental stimuli and receive input from both olfactory (odor) and trigeminal (irritant) pathways [95–97]. In order to verify this model, two electroencephalographic (EEG) studies have found that IEI subjects, relative to healthy controls, display either increased absolute delta power or greater variability in alpha power following repetitive chemical exposures [98,99]. Moreover, IEI patients manifest faster reactions over time as ascertained by the potential of an auditory event [59].

Other neurophysiological studies point out that subjects with high IEI manifest lower sleep efficiency and lower rapid-eye-movement sleep percentage than subjects with low IEI as assessed by a polysomnographic study [100]. Another study reveals that IEI patients display a greater alpha pattern at resting baseline than healthy controls as ascertained by EEG [101].

### *Toxicological, neurochemical, and neuroendocrine findings in IEI subjects*

Concerning toxicological findings, most studies have not obtained significant differences between IEI subjects and healthy controls [102]. There is only one study indicating the increased elevation of mercury levels in IEI patients compared to healthy controls [103].

Regarding neurochemical and neuroendocrine findings, several studies demonstrate that IEI patients exhibit a more positive symptomatic response (panic attack criteria) to sodium lactate compared to healthy controls [44,104]. Furthermore, a single study shows that IEI pathology is not associated with vitamin deficiency or thyroid dysfunction [105].

## Disability in IEI Subjects

IEI subjects exhibit more psychosocial (social isolation), occupational (unemployment), and/or medical (increased service use) impairment than healthy controls, even after adjustment for somatic and psychiatric morbidity [5,9,11,29,76,94,106,107]. Studies also underline that this overall disability is mainly associated with the strenuous avoidance of perceived triggers [57,108–110]. Finally, follow-up studies (up to 9 years) indicate that IEI pathology

tends to be stable over time. Hence, reported disability is usually chronic [11,54,111].

### Treatment of IEI Subjects

#### *Psychological treatment in IEI subjects*

Because of the extremely resistant cognitions regarding threatening environmental stimuli, IEI subjects raise some concerns when attending psychotherapy. Initially, a therapeutic alliance should be promoted before using some confrontative methods [112,113].

Concerning psychological techniques, several case reports indicate decreased phobic avoidance using *in vivo* desensitization. Conversely, cognitive restructuring has obtained limited results for cognitive distortions concerning threatening environmental substances [73,114]. This last finding is in line with experimental research (provocation studies) in which subjects who had not adequately detected mobile phone signals did not change their attributions after being provided with accurate feedback [115]. Furthermore, some randomized controlled trials underline that mindfulness-based techniques may decrease psychological distress and improve sleep quality and coping strategies [116–118].

#### *Psychiatric treatments in IEI subjects*

Data from psychiatric treatments for IEI subjects are limited to case reports. For example, some authors underscore some benefits from selective serotonin reuptake inhibitors (SSRI) [114,119,120]. Another study indicates that electroconvulsive therapy (ECT) may reduce symptom severity [121]. Other treatments such as transcranial magnetic stimulation are still in progress [122].

#### *Other treatments*

Alternative therapies such as aromatherapy have yielded no significant improvements on clinical symptoms so far [123]. Similarly, there is a lack of clinical trials concerning the use of other somatic treatments (e.g., antihistamines) [124].

From an ecological approach, rehabilitation interventions may remove “environmental” barriers affecting the employment outcomes among people with IEI [125]. However, the risk of iatrogenicity should be considered when implemented [126].

### CONCLUSIONS

This systematic review sought to delineate the main characteristics of IEI patients and compare them with healthy controls. The most relevant conclusions are as follows: (i) Women are at high risk for IEI. (ii) Subjects with IEI exhibit higher rates of internalizing disorders (especially somatoform disorders) as well as neurotic personality traits. (iii) Subjects with IEI do not manifest a consistent pattern of neurocognitive deficits. (iv) IEI may

be triggered by chemical exposure in some vulnerable subjects. (v) IEI subjects display higher concerns regarding chemical environmental threats and pay more attention to related stimuli. (vi) Classical conditioning as well as sensitization processes may explain generalized reactions to several chemical stimuli. (vii) Cultural modeling may play a role in the phenomenology of IEI. (viii) IEI subjects are not more sensitive to chemical substances but are more easily disgusted and display an increased activation of anterior cingulate cortex during olfactory stimulation. (ix) Some genetic polymorphisms may confer greater susceptibility for IEI. (x) There is no consistent evidence concerning toxicological findings involved in IEI. (xi) Higher impairment among IEI subjects is mainly associated with a phobic avoidance of context stimuli. (xii) Evidenced-based treatments are limited and are mainly focused on reducing dysfunctionality and distress.

Overall, these inconclusive findings support a biopsychosocial model for IEI. Likewise, these data also suggest that IEI may be conceptualized as a somatoform disorder rather than an anxiety or psychotic disorder [127].

### Limitations and Directions for Future Research

First, more prospective studies are needed in order to determine whether comorbid mental disorders and cognitive processes are either predispositional or maintenance factors for IEI. Second, studies recruit IEI subjects according to different clinical criteria as well as methods of ascertainment. Hence, a generalization of results is limited by these methodological flaws. Third, studies focused on disgust sensitivity should be encouraged in order to clarify its role in IEI subjects during olfactory stimulation [128]. Fourth, there is a lack of studies concerning the role of pregnancy as a trigger event for IEI [129]. Fifth, successful treatments for core cognitive distortions are still not available [130].

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