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Review Article

Idiopathic environmental intolerances (IEI): From molecular epidemiology to molecular medicine

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Inherited or acquired impairment of xenobiotics metabolism is a postulated mechanism underlying environment-associated pathologies such as multiple chemical sensitivity, fibromyalgia, chronic fatigue syndrome, dental amalgam disease, and others, also collectively named idiopathic environmental intolerances (IEI). In view of the poor current knowledge of their etiology and pathogenesis, and the absence of recognised genetic and metabolic markers of the diseases. They are often considered "medically unexplained syndromes",. These disabling conditions share the features of poly-symptomatic multi-organ syndromes, considered by part of the medical community to be aberrant responses triggered by exposure to low-dose organic and inorganic chemicals and metals, in concentrations far below average reference levels admitted for environmental toxicants. A genetic predisposition to altered biotransformation of environmental chemicals, drugs, and metals, and of endogenous low-molecular weight metabolites, caused by polymorphisms of genes coding for xenobiotic metabolizing enzymes, their receptors and transcription factors appears to be involved in the susceptibility to these environment-associated pathologies, along with epigenetic factors. Free radical/antioxidant homeostasis may also be heavily implicated, indirectly by affecting the regulation of xenobiotic metabolizing enzymes, and directly by causing increased levels of oxidative products, implicated in the chronic damage of cells and tissues, which is in part correlated with clinical symptoms. More systematic studies of molecular epidemiology, toxico- and pharmaco-genomics, elucidating the mechanisms of regulation, expression, induction, and activity of antioxidant/detoxifying enzymes, and the possible role of inflammatory mediators, promise a better understanding of this pathologically increased sensitivity to low-level chemical stimuli, and a solid basis for effective individualized antioxidant- and/or chelator-based treatments.

Keywords: Antioxidants, Chelators, Genetic polymorphism, Idiopathic environmental intolerances, Redox imbalance

Introduction

Idiopathic environmental intolerances (IEI)

Pioneer modern studies on hypersensitivity to chemicals date back to the mid 1950s, although reports existed since late '80 about a condition defined as *neurasthenia*[1]. During the last decades, concern for environmental intolerances has been rising, partly due to increased attention to the pathogenetic role of pollution and stressful lifestyles. A consistent number of studies on different environment-associated idiopathic conditions, including multiple chemical sensitivity (MCS), fibromyalgia (FM), chronic fatigue syndrome (CFS), sick building syndrome (SBS), and others, has therefore appeared[2]. To address this wealth of inhomogeneous clinical data, the World Health Organization has labelled as "idiopathic environmental intolerances" (IEI) those multi-organ conditions[3], with special reference to MCS. They are described as aberrant responses to a wide spectrum of potential environmental-borne organic or inorganic chemicals, through airborne or other routes of exposure. The onset of clinical symptoms connected with IEI is related to different physical, chemical or biological factors mainly of environmental origin, such as xenobiotic chemicals and metals, radiations, iatrogenic factors, specific food, microbial and environmental allergens, and endotoxins. Majority the symptoms are overlapping among the different chronic idiopatic conditions of MCS, FM, CFS, SBS, irritable bowel syndrome(IBS), Persian Gulf War veteran syndrome, "amalgam disease", electric hypersensitivity, burn-out syndrome, etc.[4,5] (Table 1). Moreover, CFS, FM and the Gulf War syndrome show specific markers and clinical signs, which are co-morbid with autoimmune diseases like systemic lupus erithematosus and rheumatoid arthritis[6,7]. Nevertheless, the question as whether IEI have to be

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considered diseases or plain clusters of symptoms has remained unanswered so far[8,9], since patients rarely display recognized dysfunctions of the immune system, or IgE-based allergic reactions.

Due to the lack of clear-cut diagnostic criteria and absence of proven pathogenic mechanisms, these diseases remain in most cases neglected by the medical community, which is unable to offer any therapeutic advice. This has generated the collective label of "medically unexplained symptoms" [9,10]. The absence of therapeutic guidelines leaves space for unregulated and unrecognized treatment protocols, devoid of satisfactory levels of safety, compliance and clinical efficacy assessments, raising further ethical issues for the medical community. Main difficulties towards a clinical consensus about these pathologies lie in the wide array of symptoms allegedly linkable to environmental triggers exposure, in the diversity of subjects affected, reacting on the basis of individual sensitivity. The large spectrum of possible triggers (Table 2) and the absence of dose-dependent reactions also generate methodological difficulties and bias in provocation studies. Finally, there exist conceptual difficulties in attributing a disease *status* to chemico-physical stimuli delivered in low concentrations, far below the respective reference levels well established for environmental toxicants. In spite of all documented scepticism, the need to address these issues systematically, to provide patients complaints

Table 1 — Symptoms characterizing idiopathic environmental intolerances (IEI).

Symptom classification [1]	Syndrome
Head/eye-related	MCS – GWV – CFS – FM – SBS – SHS – electric hypersensitivity
Cognitive / Behavioural	MCS – GWV – CFS – SBS – SHS – electric hypersensitivity
Affective	MCS – GWV – CFS – electric hypersensitivity – dental amalgam disease
Neuromuscular	MCS – GWV – FM – CFS
Musculoskeletal	MCS – GWV – FM – CFS
Skin-related	MCS – GWV – electric hypersensitivity – SBS – SHS
Genitourinary	MCS – GWS – burnout syndrome
Gastrointestinal	MCS – GWS –IBS – FM – electric hypersensitivity
Heart/Chest-related	MCS – GWV – CFS
Airway or mucous membrane	MCS – GWV – SBS – SHS – dental amalgam disease – electric hypersensitivity
Immunological	CFS – FM – MCS/ – dental amalgam disease – burnout syndrome

[1]According to Miller and Piroda, modified
MCS = multiple chemical sensitivity; IEI = idiopatic environmental intolerances; CFS = chronic fatigue syndrome; FM = fibromyalgia; IBS = irritable bowel syndrome; SBS = sick building syndrome; SHS = sick house syndrome; GWV = Gulf War Veterans

Table 2 — Triggers implicated in the symptom onset and recurrence in the subjects with idiopathic environmental intolerances (IEI).

Type of Trigger	Syndrome
Chemical	
All perfumed substances	MCS – GWV
Volatile organic solvents	MCS – CFS – SBS – SHS - GWV
Petroleum-based products	MCS
Smokes (tobacco, smog, vehicle exhaust, barbecue grill, etc.)	MCS – GWV
Pesticides, agricultural chemicals	MCS
Chlorinated water	MCS
Heavy metals	dental amalgam disease
Cosmetics/soaps	MCS
Perfumes / Deodorizers	MCS
Detergents (all)	MCS
Household chemicals/detergents/bleachers	MCS
Fresh ink/toner/office machines	MCS – CFS – SBS
Aldehydes	MCS
Fabric products	MCS – SBS – SHS
Carpet products	MCS
Building materials / glues / paints	MCS – SBS – SHS
Selected foods	MCS – IBS
Anaesthetics	MCS – burnout syndrome
Psychotropic drugs	MCS
Anticancer chemotherapics	MCS – CFS
Other pharmaceutical drugs	MCS – FM – CFS
Biocompatible materials including nanoparticles and silicone	MCS- FM-CFS
Biological	
Fungal antigens and fungal toxins	MCS – CFS
Yeasts and yeast antigens	IBS
Viral and bacterial infections	FM – CFS
Single or multiple vaccinations	FM – CFS – GWV
Physical	
Electro-magnetic fields	electric hypersensitivity
Telephone and wireless lines	electric hypersensitivity
Video display units	electric hypersensitivity
Irradiations (UVR, XR, Vis)	MCS – CFS – FM
Psychological	
Stressful events	MCS – FM – CFS – burnout syndrome – GWV – IBS
Panicogenic triggers	MCS – FM – CFS

For legend seeTable 1

with adequate responses, has been emphasised in the last two decades by the medical community[11].

Multiple chemical sensitivity—It is described as a multi-organ condition, where recurring symptoms are muscular weakness and fatigue, confusion and memory loss, minor and major depression, general anxiety, panic disorders and post-trauma distress, respiratory distress, chronic bronchitis and asthma, gastrointestinal tract malfunction, and migratory joint pains[5]. Exposure to even negligible concentrations of common odorous substances, including organic volatile compounds, perfumes, fresh paint, cleaning chemicals, print and toners, new carpeting, and numerous other products, are self-reported as connected to the onset and perpetuating of recurrence of symptoms by hypersensitive MCS patients[12,13]. A particular role of olfactory function is under debate[14]. The diagnosis is set on the basis of anamnestic criteria and thorough enquiry on possible trigger exposure[15,16]. Due to the prevalence of neurologic impairment, and lack of recognized molecular/biochemical markers for MCS, clinicians incline to classify it among the somatoform disorders or other psychiatric disturbances, on the basis of several studies demonstrating unsatisfactory results of provocation studies[17,18].

Fibromyalgia—is a chronic pain syndrome, characterized by widespread inflammatory rheumatic disease with non-articular musculoskeletal pain, acute febrile illness, paresthesia, fatigue, primary sleep disorders, memory and concentration impairment[19], major depressive disorder, migraine, and irritable bowel syndrome[20], often leading to working and social inability. The unavailability of specific anatomic, hystological or molecular disease markers complicates the diagnosis. Environmental factors may trigger the development of the chronic pain disorders in individuals with a genetic predisposition[21]. Intolerance to certain foods and chemicals has also been implied in FM onset.[22]

Chronic Fatigue Syndrome—It is diagnosed on the basis of unexplained disabling fatigue lasting for at least 6 months and not healing with rest, along with several non-specific accompanying symptoms, including disordered sleep physiology and non-restorative sleep syndrome, diffuse myalgia, cognitive and behavioural impairement[23]. The patho-physiological mechanism of CFS is still unclear. Common molecular and cellular features of the disease include altered cytokines profiles, decreased function of natural killer cells, presence of autoantibodies, and a reduced response of T cells to mitogen and other specific antigens[24]. Aspects of cytokine and cellular immune functions are shown to be related to the sleep-wake system[25]. The activation of peripheral, central inflammatory and oxidative stress pathways has been recently implied in the etiology of CFS functional symptoms[26].

Amalgam disease—The disease is a widely controversial disabling condition, occurring in allegedly metal sensitive subjects, who carry dental amalgam fillings, which contain almost 50% mercury, along with tin-copper-silver and zinc. These materials, used since almost two centuries in dental care, release Hg vapours, though in daily doses far lower than those known to induce neurological symptoms[27]. This potential Hg chronic intoxication has been connected with a wide variety of symptoms, ranging from oral mucosal and cutaneous signs, to persistent fatigue and autoimmune diseases. Few evidences have also linked dental amalgam to increased risk of multiple sclerosis, the association with Alzheimer or Parkinson disease being far less documented[28]. Studies on the dentist category have neither documented abnormal death or disease rates, nor any disability susceptible of association with Hg vapours[29]. In particular, no consistent associations were found between urinary Hg concentration, or the chronic index of Hg exposure, and any category of neurological symptoms[30]. Till date, this disabling complex of symptoms remains unrecognized by both clinical community and legal entities.

Electro-magnetic hypersensitivity—This condition is perceived as consequent to exposure to environmental electro-magnetic stressors[31], followed by recovery through the complete isolation from triggers. Subjects complain functional symptoms of the nervous system, i.e. dizziness, fatigue, headache, difficulties in concentration, memory problems, anxiety, depression, respiratory and gastrointestinal symptoms, eye and vision symptoms, palpitations, chronic fatigue, fibromyalgia, skin inflammatory and allergic reactions of face, hands and forearms, and other disorders, in the absence of organic pathological signs. This syndrome is subjectively attributed to the exposure to frequencies in the radio, microwave, kilohertz, and extremely low-frequency ranges of electro-magnetic fields or radiofrequencies, including the so-called “dirty electricity”, that is the pollution due to poor isolation of electric wires and telephonic lines, wireless devices, wi-fi, etc., though no

conclusive demonstration of causal relationship has been drawn so far. These EMF sources vary considerably but are in most cases, far below levels known to cause physiological changes in animal models[32]. Most of the initial reports from Scandinavian authors deal with dermatological symptoms, subjective, such as itching or burning, and objective, i.e. redness and dryness. These symptoms appear after individuals begin working with video display units, and decrease during absence from work[33]. Electric pollution has been connected in anecdotic studies encouraging deeper investigation, to increased risk of chronic and degenerating diseases, including asthma, diabetes, and multiple sclerosis[34]. As in the case of Hg intoxication, convincing evidences are available only on acute and chronic health disorders deriving from professional exposures to high intensity fields, in electric power plants,[35] but no data are available on sub-acute exposures below recommended reference levels, occurring in the civil life[36]. In addition, data available on the exposure levels self-reported by subjects, or evaluated in studies, are extremely meager. One Swedish study tried to connect perceived fatigue to alterations in cholinesterase activity, finding no correlation[37]. Several controlled provocation studies failed to discriminate between healthy subjects and subjects claiming to be hyper-sensitive to electric or phone signals, in perceiving exposure to low-dose effective or sham triggers[38,39]. In general, case-control studies, as well as some good but limited double-blind trials, have not found any clear relationship between claimed symptoms and exposure to EMFs[40]. In spite of controversial results, the concern of physicians in some countries seems to be widespread[41,42].

Here again, as in the other conditions described, the almost complete absence of consistent patho-physiological markers, and of validated tests, is the main hindrance to the diagnostic assessment of a perceived disease that can often result invalidating. Various factors have been identified as methodological bias in the provocation studies on IEI. In the case of electric hypersensitivity these factors include inappropriate selection of statistical power, effect of background EMF, inappropriate lag-time between trigger administration and effect monitoring, etc[43]. Psychological conditioning through media information may represent a bias, as well as the frequently occurring patient's disatisfaction for mainstream medical approaches[44], and therefore psychological factors should better be included in data analysis[45].

Environmental toxicity: Impairment of the chemical defensive system

The exposure to environmental pollutants and toxicants is a crucial challenge for the human metabolism which has to adapt not only to the chronic non-physiological load of conventional compounds, such as cosmetics, detergents, preserving agents and eccipients, pharmaceutical drugs, but also to entirely new molecules, e.g. slow degrading nanomaterials for medicinal use[46].

A concerted action of constitutive and inducible, strictly regulated, protective pathways enables adaptation to the rapidly changing environment. This metabolic system defending towards chemicals has presumably evolved very early in primitive eucariots and lower plants, before immune system developed to handle high-molecular weight antigenic molecules, microbes and foreign cells. The chemical defensive system detoxifies low-molecular weight organic and inorganic compounds, including heavy metals, as well as endogenous non-protein signaling molecules, mediators of inflammation, degradation products, and toxic by-product of cellular metabolism[47].

Recent advances in toxicogenomics have highlighted the role of inherited genetic traits in the individual susceptibility to both xenobiotics and toxic endogenous metabolites[48]. Evolutionary, a complex array of gene families codes for enzymes of specific molecular pathways has specialised to metabolize and clear toxic chemical substances, and to repair molecular consequences of chemical damage. Reactive oxygen species (ROS) are a active part of the detoxification process, both in exposed epithelia and in internal tissues, with a double role of biosensors of environmental/endogenous stressors with signalling function, and of by-products of toxicant-induced oxidative damage and of toxicant detoxification pathways[47,49-51], their concentration being tightly regulated by a complex redox homeostatic control.

Chemical that are not directly cleared from cells by active efflux proteins[47] are subjected to biotransformation by oxidative phase I enzymes in the cytoplasm, primarily by cytochrome 450 enzymes – CYPs-, flavoprotein monooxygenase, amine oxidases, xanthine oxidase, frequently followed by phase II reductive or conjugative modification through glutathione-S-transferases (GSTs), UDP-glucoronosyl

transferases (UGTs), catechol-*O*-methyl transferases (COMT), N-acetyl transferases (NATs), epoxide hydrolase, and many others[52]. ROS generated as by-products of phase I reactions are rapidly reduced to non-toxic "physiological" levels by antioxidant enzymes, superoxide dismutase, catalase, glutathione peroxidase, and peroxiredoxins, and by low-molecular weight antioxidants, reduced glutathione, uric acid, ascorbic acid, ceruloplasmin, and others. In case of challenge by higher-than-normal concentrations of exogenous or endogenous toxicants, the interaction with cellular membrane or nuclear receptors induces the expression of an array of stress responsive genes, coding for bio-sensoring, signal transmission, and response elements. Superoxide anion-radical, hydrogen peroxide, lipid peroxides, and other ROS come again into play, mediating the activation of two pathways, protein kinase (PKs) cascades, and/or transcription factors (nuclear factor κB (NFκB), activator protein-1 (AP-1), and antioxidant response element (ARE)-binding proteins), to start gene transcription and protein synthesis of the phase I, phase II, and antioxidant enzymes[47,50,51].

This complex detoxification system is a common target of inherited or functional genetic defects and epigenetic factors. Alterations of the system might lead to incomplete detoxification of exogenous/endogenous toxins or/and to excessive generation of toxic by-products ("Poor Metabolizers" - PM), or to higher-than-normal rates of metabolization, in subjects with hyper-functional genes, possibly duplicated or multiplicated ("Extensive Metabolizers" - EM).[53] The consequences of these genetic or functional alterations are not univocal, and deserve thorough clinical interpretation, being potentially detrimental or beneficial, depending on the biological function and relative toxicity of the parent compound and of its metabolites. These polymorphisms also affect individual metabolism and resistance towards therapeutic drugs. Further complications for clinical correlation of gene polymorphism with clinical settings occur in the case of detoxifying genes present in multiple classes, requiring multivariate analysis.

Pathogenesis of IEI: Genetic and epigenetic defects of Phase I and II enzymes

In spite of the wealth of studies produced on phase I metabolizing enzymes in the susceptibility to environmentally induced cancers, limited and contradictory information is available on the possible role of their malfunction in non-tumor environment-associated pathologies. A first case-control research on female Caucasians demonstrated an increased risk for MCS in EM individuals, homozygous for the cytochrome P450 isoform CYP2D6, as compared to PM with inactive gene[54]. The same work documents a possible gene-gene interaction between CYP2D6 and phase II N-acetyl transferase 2 isoform, with consequent elevated risk of MCS development in rapid metabolizers for both enzymes. NAT2 polymorphism and homozygous deletions of M1 and T1 GST genes were again recently significantly correlated with proneness to MCS[55], confirming that multiple polymorphisms of drug metabolizing enzymes predispose individuals to exaggerated chemical sensitivity[53]. CYP2D6 isoform is a key enzyme in the metabolism of most anti-depressant and antipsychotic drugs[56]. The PM genotype for CYP2D6 was also proposed as a negative prognostic factor in the development of FM[57]. In spite of the data on genetic and functional peculiarities of drug metabolizing enzymes in MCS subjects[54,55], other studies exclude any molecular basis for this condition[58,59], claiming inconsistency of results due to limitations in the size of study groups, and methodological bias in patient diagnosis and/or in genetic analysis.

The three main GST families, the soluble ones located in cytosol and mitochondria, and the membrane associated one in microsomes, possess a number of enzymatic and cell signaling regulating functions connected with the detoxification of potential carcinogens and cytotoxic agents[60]. GSTs, and especially GST P1-1, are in fact over-expressed in a variety of malignancies, and correlated to resistance to anticancer agents and chemical carcinogens[61]. GSTM1 is strongly connected with the early onset of various diseases based on impaired carcinogen detoxification[62,63]. GST polymorphisms may reduce glutathione conjugation, one of the major protective mechanisms to modulate reactive metabolite-induced oxidative, and particularly genotoxic damage. Not only individual isoenzymes, but most importantly isoform combinations, contribute to resistance to carcinogens, antitumor drugs, environmental pollutants, and products of oxidative stress. Therefore association of polymorphisms have been correlated with MCS[55], and more recently with FM[64]. GST cytosolic activity in the olfactory epithelium, the highest in extrahepatic tissues[65], is of particular

interest for MCS, where the role of odorous triggers is strongly called into play.

Polymorphisms of catechol-*O*-methyl transferase has been investigated in IEI, in connection with the prevalence of neurological symptoms connected with anxiety, memory loss, neuro-muscular pain in IEI, FM and CFS. COMT genetic and epigenetic factors are key biochemical features in the pathologies of the central nervous system with impairment of catecholamine regulation[66]. The most studied COMT gene allelic variants, Val158Met (rs4680), a functional SNP resulting in much higher activity, is linked to the impairment of specific cognitive tasks. In neuropathic and inflammatory pain, new studies[67] suggest that COMT expression may be regulated through COMT P2 promoter, in the course of nociceptive signaling of NF-kB. As for IEI, association analysis has revealed a significant excess of the more active COMT allele (472G=V158) related to panic disorder, in particular in female patients[68]. Low COMT activity has been associated with increased pain sensitivity in subjects with perpetuating pain condition[69]. COMT diplotype, indicative for low COMT enzyme activity, has also been shown to increase the risk of chronic pain syndromes, as demonstrated in 63 patients undergoing a standardized fatigue protocol[70]. In a group of 43 CFS patients, SNPs of COMT, neuronal tryptophan hydroxylase-2, and nuclear glucocorticoid receptor NR3C1 allowed prediction of CFS with 76% accuracy[71].

Most of the publications on UDP-glucoronosyl transferase polymorphisms are referred to cancer prevention; few studies have been performed to elucidate their possible role in chemical and nutritional intolerances. UGT isoforms are localized in the inner side of the endoplasmic reticulum membrane, and are committed to catalyze the conjugation with uridine dipospho-glucuronic acid of different xenobiotics and endobiotics, drugs, chemical toxicants, carcinogens, phytochemicals, steroids, bilirubin, thyroid hormones, bile acids, fatty acids, prostaglandins, etc. UGTs are highly expressed in extra-hepatic tissues committed to xenobiotic absorption, distribution, metabolism and excretion, i.e. intestine, esophagus, lung, kidneys, and nasal epithelium[72].

The activity of three UGT isoforms is influenced by thyroid hormones. This could be relevant to IEI, where a significant incidence of thyroid hormone dysfunction including autoimmune thyroiditis is observed (unpublished data), or of increase of the stress-sensitive thyroxin hormone[73], although some studies deny any role for thyroid hormones[74,75]. Several other clinical features characteristic for IEI, such as anxiety or depression, and poor quality of life scores may theoretically in part be ascribed to impaired UGT metabolism of thyroid hormones[76], although no direct evidences are available so far.

Concerning other possible malfunctions of the detoxifying enzymes in IEI, the genetic or acquired alterations of peroxide detoxification deserve special attention. Catalase, selenium-dependent glutathione peroxidases (GPXs) and thioredoxin-dependent peroxidases (peroxiredoxins, PRXs) are crucial enzymes in the protection from oxidative damage generated by hydrogen peroxide and lipid peroxides. Distinct mutations in the catalase gene (the G to A transition at the fifth position of intron 4, a splicing mutation, and the deletion or insertion of nucleotides in the coding regions) result in a complete acatalasemia, bearing severe health outcomes, including increased risk of diabetes mellitus[77]. Detailed epidemiological studies suggested that individuals with lower-than-normal catalase activity are at high risk of the premature onset of age-related degenerative diseases[78]. In view of the growing amount of data available on H_2O_2 and lipid peroxides hyper-production in different environmental intolerances. The role of polymorfisms of catalase, different forms of GPxs and PRXs in the individual susceptibility and in the pathogenesis of non-tumor environmental diseases require further investigation.

Pathogenesis of IEI: Role of oxidative stress and inflammatory mediators

Availability of data concerning the involvement of chronic oxidative damage in the induction and perpetuating of symptoms in functional IEI syndromes has been growing in the last decade, although still limited mainly to CFS and FM conditions. Concerning CFS, early observations documented oxidative damage to DNA and lipids in biopsies from the *vastus lateralis* muscles, associated to adaptive up-regulation of GST activity[79]. Later studies always on patients at rest, registered elevated levels of malonyl dialdehyde[80], F2-isoprostanes[81], protein carbonyls[82], low serum α-tocopherol[83], lower-than-normal levels of reduced glutathione (GSH) and cysteine[84], and lower-than-normal total antioxidant capacity and vitamin E plasma levels, with increased

lipoperoxidation markers, in patients with mild Mg deficiency[85]. Spontaneous and stimulated production of NFkB, cyclo-oxygenase (COX-2) and inducible NO synthase (iNOS) induction in peripheral blood lymphocytes of 18 CFS patients was significantly increased *vs.* matched controls[84], and correlated to symptom severity score, further documenting the putative role of inflammatory response system and oxidative/nitrosative damage in the underlying mechanism of this functional syndrome[26]. In the context of redox imbalance, metal ion toxicity has been documented by increased levels of methemoglobin formation in FCS erythocytes[86], consistent with the observed impairment of its physiological reducing agents GSH and cysteine. Data on oxidative and nitrosative stress were partly correlated with CFS specific clinical symptoms, although confounding overlapping risk factors, such as obesity[81], hypertension, smoking, were not taken into account in all studies.

Data on oxidative stress in FM are limited and controversial[87]. FM patients were shown to possess peculiar oxidative stress features, such as altered distribution and metabolism of coenzyme Q_{10} in the blood cells and muscular tissue, with higher than normal plasma concentrations, presumably an adaptive protection mechanism[88]. Significantly increased spontaneous H_2O_2 release from circulating granulocytes[88], and elevated plasma levels of oxidation markers were reported[89] and negatively correlated with depression scales. Interstingly, the patterns of redox imbalance and antioxidant protection display relevant differences between FM and CFS, as regards ubiquinol tissue levels and isoprostane urinary excretion, not significantly different in FM group *vs.* controls[87].

Chronic peroxynitrite hyperproduction has been implicated as a common etiologic factor for CFS, MCS, FM, and post-traumatic stress disorder[90]. Elevated peroxynitrite levels may cause mitochondrial dysfunction, lipid peroxidation and, by positive feedback, elevated pro-inflammatory cytokine levels, in a vicious cycle inducing NO and superoxide production, with additional peroxynitrite formation. Further, the theory is not conflicting with other mechanisms proposed for MCS, namely neural sensitation, neurogenic inflammation and pophyrin pathway abberrations[91]. This mechanism has been only indirectly confirmed in MCS patients. *In vivo* studies have not as yet unequivocally confirmed the supposed increased NO levels in FM or CFS or other environmental intolerances.

Cytokine patterns have been analysed in different IEI conditions, and deserve more extensive investigations in those environmental intolerances sharing the frequent features of chronic inflammation with distinct alterations of redox homeostasis. Cytokines may be involved in diverse clinical manifestations of interest for IEI, such as fatigue, fever, sleep, pain, stress, and persistent aching. Functional and biochemical overlapping of IEI with systemic lupus erythematosus[6] and other autoimmune diseases also sustain the feasibility of an immunologic approach, although currently results for MCS are largely controversial[92]. Dysregulated profiles of pro-inflammatory cytokines have been reported in a number of studies on CFS and FM, with the recurrent feature of chronically increased circulating levels and *ex-vivo* spontaneous release from leukocytes[93], also in connection with recurrent sleep loss[94]. Interestingly, impaired TNF-α, IL-6, and heat shock protein release were found in CFS patients following maximal cycling exercise, findings that were positively correlated with plasma TBARS increase[95].

Current therapeutic approaches and future perspectives

Consequent to the limited knowledge of etio-pathogenetic mechanisms, the environmental borne syndromes here described almost entirely lack clinical *consensus* regarding diagnostic and, most importantly, therapeutic guidelines.

In the present review the most relevant information supporting the hypothesis of an impairment of the chemical defensive system in the onset and clinical course of these chronic invalidating conditions have been collected. IEI most probably bear both genetic and metabolic components. Up-to-date, specific polymorphisms have been identified in the genes encoding for phase I and phase II detoxifying and antioxidant enzymes, and for their receptors and transcription factors, modifying gene activity and regulatory properties, and possibly representing main determinants of individual metabolizing capability. On the other hand, individual peculiarity of adaptive response to chemical stressors may be determined at the epigenetic level through the direct modification of biologically relevant macromolecular targets.

The difficulties connected with genetic screening are related to costs, interpretation and need for more research on innovative drugs delivering appropriate

metabolizing enzymes. Individual capability of adaptive response to chemical stressors may be determined at the epigenetic level through the direct interaction of these substances and their metabolites with biologically important molecules and cellular membranes. Chronically persistent toxic compounds may in fact chemically modify proteins to form auto-antigens, as suspected on the basis of symptom overlapping with classical autoimmune diseases[6,7].

The most urging concern about IEI clinical management is the complete lack of targeted drugs, resulting in an unregulated and wide array of experimental protocols, including environmental medicine techniques, holistic therapies, individualized antioxidants or immune modulator nutritional supplements, detoxification techniques, etc. (Table 3). Almost all approaches are devoid of any documented rationale validated *in vivo*, and have never been controlled for safety and efficacy *vs.* placebo in controlled clinical trials. Based on the limited information so far available, treatments are prescribed in an allegedly individualized fashion. These approaches are often uncorrelated with effective biochemical *status* and genetic predisposition of patients, and not thoroughly followed-up for compliance, efficacy, and adverse effects monitoring.

Since IEI, and in particular multiple chemical sensitivity, are commonly regarded as psychiatric or somatoform disorders, in many countries patients are prescribed psycho-active or pain-killer drugs with antidepressant, anxiolytic, analgesic, myorelaxant actions, without any preventive toxicological screening. Data acquired on polymorphic genes for drug metabolizing enzymes, affecting the metabolic rate for a number of psychotropic medications[55,56] raise a strong warning on the risk of severe adverse reaction in metabolically impaired patients. However, to our knowledge no studies have monitored so far the frequency of adverse reaction to psychotropic drugs in subjects complying with diagnostic criteria of any of the various IEI. These reactions are frequently occurring, as documented in a study on patients self-reported reactions to treatments in MCS[96].

Collectively, available data provide indirect evidence that functional or/and genetic defects of endogenous enzymes detoxifying H_2O_2, lipid peroxides or stable toxic products of lipid peroxidation may cause chronic oxidative stress and consequent metabolic alterations characteristic for the patients with IEI. Damage most likely occurs due to chronic exposure to ambient doses of environmental toxicants, therefore presumably involving specific detoxification pathways, so far still unidentified, displaying very high affinity for low-dose substrates[97].

Table 3—Main categories of treatments (including non-conventional and self-prescription) reported for idiopathic environmental intolerances (IEI).

Treatment category	Treatment	Disease
Nutritional supplements	Vitamins	MCS
	antioxidants/minerals	all diseases
	raw plant extracts	MCS – FM – FCS
Prescription therapies	Psychotropic drugs	all diseases
	Probiotics	MCS – IBS
	Antimycotics	MCS – CFS
	Antiobiotics	MCS
	glutathione	MCS – FM
	hormone replacement	MCS – CFS
Psychotherapy	Psychiatric therapies	MCS – GWV
	psychologic desensitization	MCS
	cognitive-behavioral therapy	MCS – CFS
	relaxation and stress management training	MCS – FM – CFS
	cognitive therapy	MCS
	Family/group therapy	MCS
Detoxification treatments	Selected food removal	MCS – CFS - IBS
	liver/gallbladder flushes	MCS
	metal chelation	MCS – dental amalgam disease
	traditional Chinese herbal medicine	MCS – CFS
Holistic treatments	Homeopathic remedies	all diseases
	diet regimens	all diseases
Body therapies	Graded exercise therapy	MCS – CFS
	aerobic exercise	MCS – FM
	Massage	MCS – CFS
	sauna therapy	MCS – CFS - FM
	Chiropractic	MCS
	Acupuncture	MCS – CFS
Trigger removal	Trigger-free living space	MCS – CFS- IBS- electric hypersensitivity – SBS – SHS
	chemical avoidance	MCS – CFS – SBS – SHS – GWV
	living place antifungal sanitization	MCS – SBS – SHS
	dental amalgam removal	MCS
	working place change or abandon	MCS - electric hypersensitivity

For legend see Table 1

More systematic studies are needed on the regulation, expression, induction, and activity of GPxs, Prxs, catalase and GST isoforms metabolyzing 4-hydroxy-2-nonenal, to understand better pathological susceptibility to low-level external stimuli in the subjects suffering from IEI.

In this perspective, any treatment based on antioxidant or chelator principles, able to selectively prevent formation and release of excess reactive species or hydro- or lipid-peroxides, or to enhance specific detoxification pathways through ROS/RNS modulation, is to be taken into consideration for future clinical trials.

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