

Are syndromes in environmental medicine variants of somatoform disorders?

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Summary To date, relatively little is known about the etiology, pathophysiology, diagnosis, therapy, prevention and prognosis of environment-related syndromes like multiple chemical sensitivity (MCS), idiopathic environmental intolerance (IEI), sick building syndrome (SBS), chronic fatigue syndrome (CFS), candida syndrome (CS) and burnout syndrome (BS). Part of the reason is that these syndromes have not been clearly defined and classified in scientific categories distinct from each other, and that they show clinical similarities to classified somatoform disorders. Furthermore, there are at least three possible explanations for the existence of these syndromes: (1) The syndromes may result from the interaction of environmental factors, individual susceptibility and psychological factors (i.e., how they are perceived and seen by the patient); (2) they may reflect socially and culturally accepted methods of expressing distress; and/or (3) they may be iatrogenic. Despite all the uncertainties in evaluation of environmental syndromes, physicians have the duty to take the affected person's problems seriously. A comprehensive systematic classification which better accounts for these complex clinical manifestations is long overdue. Until these syndromes are well defined, the terms used for them should definitely *not* be applied to connote a specific disease process.

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INTRODUCTION

Non-specific subjective symptoms spanning various organ systems, with particular emphasis on the eyes, respiratory system, skin, and nervous system are often attributed to 'environmental illness' (1,2). It is clear, however, that the overlap in symptomatology in what patients may perceive to be 'different' syndromes is so great, that the syndromes are not distinguished by their clinical appearance, but rather by the specialist that

happens to be dealing with the patient. Some distinguish one syndrome from another not by the presence or absence of a given symptom, but by the severity, with the assumption that the most severe symptom should best characterize the illness. Idiopathic environmental intolerance (IEI) (3–5), multiple chemical sensitivity (MCS; new classification: IEI (chemical)) (3–7), sick building syndrome (SBS) (8–10), chronic fatigue syndrome (CFS) (11,12), candida syndrome (CS) (13) and burnout syndrome (BS) (14–16) are typically described as distinct from each other because of an emphasis on one symptom more than others in each syndrome and because of the varying involvement of different clinical specialists. One of the main problems is that no validated diagnostic methods are available for objectifying and quantifying the patient's symptoms. Still, only an objective quantification would allow more than a merely operational classification of these symptoms, and also conclusively

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decide whether these syndromes really do constitute entities of their own (17–21).

IDIOPATHIC ENVIRONMENTAL INTOLERANCE

At a World Health Organization (WHO) workshop in Berlin on multiple chemical sensitivity (MCS) (3–5), the expert commission concluded that there are patients who suffer from a multitude of idiopathic somatic intolerances towards environmental agents and who require professional medical help. It was suggested that the term previously used for this phenomenon, multiple chemical sensitivity (MCS), no longer be used as it implies that the cause of these disorders is known. Furthermore, no relation between exposure and symptoms has thus far been substantiated. Hence, idiopathic environmental intolerance (IEI) is considered a fitting description for these phenomena; idiopathic here means that the problem is not well defined, its cause is unknown and its pathogenesis elusive. A working definition of IEI would be that it is an acquired disorder with multiple recurring symptoms associated with various environmental agents which are tolerated well by most people and which cannot be explained by any known somatic, psychiatric and/or psychosomatic disorder (this latter part an addition by the authors) (3–5). The expert commission recommended an improved risk communication, more precise public information based on scientific findings without speculation, better IEI patient management via concerted cooperation between the various health care agencies, institutions and insurance companies, as well as WHO funding of continuous exchange of knowledge and international cooperation in IEI research (3,4,5). There are currently no specific tests for IEI, and those used in the past (e.g., immunological tests, biological monitoring, porphyria testing, neuroimaging) have not been helpful or specific.

Studies on substance burden tolerance are urgent and take priority over studies focusing on illness mechanisms. They are needed to ascertain the cause-effect relationships between IEI and potential harmful agents, for effective public health protection, and to develop prevention and therapy strategies.

MULTIPLE CHEMICAL SENSITIVITY

MCS is a pathophysiologically undefined hypersensitivity towards all sorts of chemicals at such low concentrations that healthy persons show no discernible reaction.

While the proponents of 'ecological medicine' tend to take a very broad view of MCS, Cullen (6) set down far more restrictive criteria for a preliminary diagnosis. The onset of the disorder must be marked by an identifiable

exposure which, although the patient can name it, lies below a detectable toxicological limit. Typically the patient develops a sensitivity towards various chemicals over the course of illness, or else sensitivity towards a number of chemically unrelated substances with the most varied toxicological mechanisms of action exists from the outset. The threshold values at which the symptoms are caused are extremely low, i.e., they lie below the 95th percentile of the general population. A group of core symptoms common to all patients is yet to be found.

Hypotheses on the pathogenesis of MCS are as varied as are those which link its etiology to chemicals (7). One theme common to all biogenic theories is their attempt at finding a pathogenicity of environmental chemicals with different molecular structure and toxic action even at low, toxicologically normally harmless concentrations. Especially chronic exposure to trace amounts of pesticides e.g., insecticides, herbicides, fungicides, wood preservatives, formaldehyde, organic solvents, polychlorinated biphenyls (PCBs) and heavy metals (lead and mercury) affects several organ systems simultaneously. Some authors also consider food additives, electromagnetic fields or microorganisms as potential triggers of hypersensitivity (20,22–27). One hypothesis frequently cited by 'clinical ecologists' sees MCS as an overblown immune reaction in persons with significantly increased sensitivity towards different chemicals, or else as a toxically induced loss of tolerance (TILT), as a possible cause of non-objectifiable somatic complaints (28,29).

Models of a reinforcement mechanism postulate a predisposition towards increased sensitivity in certain persons similar to that proposed by the enzyme polymorphism models of toxicology, as well as a failure of the classical toxicological dose-effect relation (30). Psychological and psychosomatic hypotheses also figure prominently in the discussion of MCS pathogenesis (31).

There are two kinds of psychodynamic models (32–34): The intrapersonal approach starts from the premise that MCS patients suffer from anxiety, depressive or somatoform disorders, the somatic symptoms being attributed the usual causes associated with these disorders, e.g., conditioning and somatosensory amplification. The second approach sees MCS as a widespread, culturally-bound explanation for non-specific somatic symptoms. There is no compelling clinical or experimental evidence for any of these hypotheses.

SICK BUILDING SYNDROME

Since the mid-1970s, the sick building syndrome (SBS) has been increasingly reported at non-industrial work-

places, especially office buildings (8,35). It is not a well-defined condition, either, but an epidemiological-operational classification assigned to the so-called building-related disorders (9,10,42), together with the building-related complaints (BRCs) or building-related symptoms (BRS) (35) and the building-related illness (BRI) (35,36). Differentiating these building-related disorders is vital both for scientific research and for dealing with them clinically, for BRI includes well-defined conditions (e.g., humidifier-caused fever, legionellosis, indoors-associated allergies and malignancies) with a relatively clear etiology, pathology, pathophysiology, diagnosis, therapy, prevention and prognosis (35,36). The same applies to the BRC or BRS, which – unlike the epidemiologically defined SBS – is an operational classification centered around the individual (35). Unfortunately, the terms SBS, BRI, BRC and BRS are often used interchangeably, which can be quite confusing (37). This hazy, imprecise choice of terms and in the absence of a clear definition are a constant cause of criticism and doubt regarding the existence of SBS (38–40). Nor does it help that the intensity, frequency, number of symptoms, the course of illness and timeframe of SBS have not been properly defined (41,42).

Still, there is epidemiological evidence for the existence of SBS worldwide (9,10,43–45). When evaluating SBS reports, it must be kept in mind that a certain background prevalence of SBS-associated complaints is also seen in buildings not affected by SBS (so-called healthy buildings) (46,47). Exceeding this background prevalence, which lies in the range of 10–20% (9,10,36), is one of the criteria for diagnosing SBS.

It is known, however, that SBS has been on the rise since the mid-1970s, with isolated reports from the 1960s (47,48), and it seems that all Western metropolises are affected. Up to 30% of newly erected or renovated buildings are said to exhibit SBS. According to estimates, 20–30% of office workers in industrialized nations – more than 50% of all employees in these countries – complain of indoors-associated problems (9,10,43,47,48). Epidemiological data on SBS in Germany still are sparse. In the early 1980s, at least one fifth of 2.5 million office workers in West Germany (including West Berlin) who worked in climatized buildings reported a number of the complaints associated with SBS (49). Preliminary research of the ProKlimA study on 613 persons in one building showed that 30–40% of all employees had such problems (50). In 1995 the worker's syndicate reported that of 19 million office workplaces in Germany (about 3 million climatized), 3.8 million 20% were affected by SBS (51). In 1996 Petrovitch estimated that at least one million in Germany were affected to a greater or lesser extent by SBS-like symptoms (52). Most international studies were done on office buildings, but SBS was also found in kindergartens,

schools and hospitals (9,10,53–57). Possible causes include physical (e.g., ventilation rate, air velocity, temperature, sound, lighting), chemical (e.g., tobacco smoke, suspended and settled dust, inorganic gases like carbon dioxide, carbon monoxide, nitrogen dioxide, less so sulfur dioxide, also a number of volatile organic compounds and pesticides), biological (e.g., bacteria, mould) as well as individual and psychosocial factors (e.g., female gender, allergies, familial atypical disposition, growing up in an urban environment, exposure to tobacco smoke during childhood, living in a city, recently painted surfaces near home, psychological stress at the workplace) (9,10,43,44,58).

A detailed and critical review by Mendell (45) of epidemiological SBS studies from 1984 to 1993 turned up four environmental risk factors – type of ventilation (artificial), air flow rate $<10\text{ l s}^{-1}$ and person, several workers sharing a room or work area, visual display terminal (VDT) work – and three individual and psychosocial factors: female gender, allergies and/or asthma, as well as job dissatisfaction. Strategies for tackling SBS were developed based on international experience (43,59,60). A detailed account is given by Neuhann and Wiesmüller (61) and by Wiesmüller (62). In cases where SBS is suspected, the recommended procedure is to begin with the simple standardized Örebro questionnaire developed by the Medicine Clinic of the Örebro Hospital (Sweden) which already has been validated in several countries (46,63–66). Further questionnaires available include those by Kröling (49,67–70), Seeber et al. (71), Bullinger et al. (72,73) and Wiesmüller et al. (74,75). For cases of suspected SBS in kindergartens and schools, the Medicine Clinic of the Örebro Hospital also has questionnaires for parents of pre-school and grade school children, as well as for high school students. In addition to questionnaires, symptom diaries can be kept (75–77).

Specific methods for demonstrating a relation between symptoms and SBS are not available yet, or not ready yet to be employed in the field (62,78–80). Operationalization and quantification of these symptoms is essential the definition of SBS. Furthermore, negative investigations of SBS-associated symptoms must be conducted: all possible somatic, psychological, psychosomatic and psychiatric disorders and illnesses must be excluded first. Use of medication, tobacco, alcohol and drug abuse must also be considered. Since the etiology of SBS is unknown, methods for prevention are likewise unknown, although some pragmatic experience may be helpful in minimizing the risks (61,81).

In sum, it must be said that further research on SBS is needed for a clear characterization of the phenomenon. For further discussion of the topic, refer to (9,10,43,44, 48,59,82–93).

CHRONIC FATIGUE SYNDROME

CFS is a complex of symptoms characterized primarily by a severe, persisting fatigue whose causes are not well known yet. Possible triggers can include bacterial or viral infections, immunological disorders and neurological-psychiatric illnesses (94–97). The many different terms – atypical poliomyelitis, neurasthenia, chronic brucellosis, myalgic neuromyasthenia, epidemic myalgic encephalomyelitis, postviral fatigue syndrome, Icelandic disease, royal free disease, Lake Tahoe disease, yuppie flu, etc. – are evidence of the great variety of symptoms associated with this syndrome, of the hypotheses regarding its etiology, as well as the sites of occurrence of the most significant microepidemics (98). Diagnosis and differential diagnosis of CFS is quite difficult since the syndrome is not an illness in the classical sense, i.e., with a single cause (99,100).

According to Fukuda et al. (11), a diagnosis of CFS can be made if fatigue persists for six months or longer or occurs repeatedly and if it accompanied by further symptoms, such as muscle or joint pain, sore throat, swollen lymph nodes, headache, difficulties concentrating and impaired short-term memory. A precise time of onset can usually be given since the joint occurrence of several different symptoms can mark a considerable change in the patient's life, although some patients report a gradual decline in their general health. The CDC (Centers for Disease Control and Prevention) criteria modified by Fukuda et al. (11) for dealing with CFS victims help, but they are not strict enough to provide a clear profile of the syndrome.

The many hypotheses on its pathogenesis can be divided into three main groups: microbiological-immunological, endocrinological, and neurological-psychiatric. Changes in T cell suppressor function, reduced EBV-specific cytotoxic T cell activity, changes in the number and function of natural killer cells, as well as raised cytokine levels have been described. Many authors have also reported raised IgG titers against Coxsackie- and Epstein-Barr viruses. Unfortunately, these fluctuations are often only slight, and the sensitivity and specificity of serological tests allows no definitive conclusions, especially since a number of diseases can be associated with these altered titers. Virological, bacteriological and mycological tests have not shown any strong causal connection between any single infection and CFS (101,102).

The literature on the immune system and distress is extensive, and psychoimmunological interactions in CFS have been the subject of increased scientific scrutiny. Patients often report having been under great physical or psychological stress prior to the onset of CFS (100), stress which can well affect the endocrine metabolism

(103). Aside from a thorough case history and examination, a positive diagnosis of CFS also requires the exclusion of other illnesses and diseases which can cause fatigue, including:

1. chronic illnesses: neoplasias; autoimmune diseases; diseases of the organs; endocrinological, hematological, neurological, neuromuscular conditions; chronic intoxications; medication and drug addiction;
2. localized or systemic infections: Epstein-Barr virus infection; chronic active hepatitis B or C; chronic active Lyme disease; HIV infection; tuberculosis; mycoses; parasites;
3. changes in metabolism and electrolytes: absolute or functional vitamin deficiencies; selenium deficiencies; etc.
4. psychiatric disorders: endogenous depression; psychoses; bipolar illness; schizophrenia; drug abuse.

CFS can take either a chronic course or be self-limiting (104,105).

Due to the great uncertainty involving diagnosis and therapy, many researchers have called the existence of CFS into question, or classified it as a psychosomatic or psychiatric disorder without further laboratory tests.

CANDIDA SYNDROME

Over the past few years, many authors have proposed a connection between mucocutaneous *Candida* infection and non-specific abdominal and systemic problems (106–108). It is postulated that a number of factors, such as oral antibiotics, corticosteroids and estrogens, as well as a diet rich in carbohydrates or yeast can lead to an imbalance of the intestinal flora, eventually leading to an excess colonization with certain yeast, especially those of the genus *Candida*. Candidiasis is considered a cause of intermittent or persistent malaise and/or multiple extraintestinal symptoms or illnesses, including forgetfulness, difficulties concentrating, fatigue, depression, nausea, diarrhea, meteorism, constipation and tenesmus. It is believed that *Candida* spp. carry an antigen responsible for a hypersensitivity syndrome with various clinical manifestations. The constant activation of the immune system would then lead to a general immune deficiency (109–111).

In spite of the absence of controlled scientific studies which would give evidence of a *Candida* syndrome and justify such a therapy, the opinion is frequently heard that the presence of yeast, especially *Candida* spp., in the stool is pathological and that a therapy to reduce or eliminate the organisms is in order. The types usually recommended are:

- proper antimycotic therapy;
- a diet poor in carbohydrates (the main nutrient of fungi);

- probiotic therapy to restore the intestinal flora to normalcy.

It should be mentioned that at present, the *Candida* syndrome carries no diagnostic or therapeutic weight, not having been substantiated clinically or through controlled studies (110). Odds (112) reported that yeast-like fungi are found in the stool of 8–60% of healthy persons, with a weighted mean of 23.2%. For patients with different diseases and therapies, the value ranged from 5.7% to 83.1%, with a clearly higher weighted mean of 38.2%. In a randomized, double-blind study, antimycotic therapy was no more effective than a placebo (107,113). Uncritically linking hazy syndromes to the presence of yeast in the stool carries not only the risk of obscuring other, concomitant conditions which would require treatment, it could also create mycophobia in some patients (114,115).

BURNOUT SYNDROME

The burnout syndrome (BS) is not a clearly defined illness, either, but is taken as an operational classification without a generally accepted definition. This syndrome comprises somatic and psychosomatic symptoms, involving mostly the heart and the circulatory system, the gastrointestinal tract and the skeletal system, psychological symptoms like cognitive impairments and the emotional difficulties, as well as social problems such as social withdrawal and isolation. In principle, anyone can be affected, regardless of occupation or status, but BS is seen more frequently in the supporting and human services professions, such as teachers, administrators, managers and police, as well as employees at churches or charities. Solid data on this syndrome are rare (15,16,116–119).

Basically, BS shows a slow, gradual course and progresses in three stages. The first stage, often termed irritation, is characterized by feelings of unfounded fear and somatic problems along with tension, lack of energy and drive. The second stage, frustration, is characterized by dissatisfaction with the job and with oneself and anger which may explode in spontaneous aggression, irritability and impatience. The somatic symptoms become stronger, and often times the patient can only relax after taking alcohol or tranquilizers. During the third stage, desperation and decisions to change the job are frequent. This stage is characterized by feelings of inadequacy and impotence, blaming oneself, withdrawal, apathy, mistrust and cynicism. A more comprehensive description can be found elsewhere (15,16,119–121).

Three factors are essential in the development of BS: the workplace, individual characteristics, and interpersonal relationships. The workplace, or the general environment at work, is associated with the kind and the intensity of work overload, lacking possibilities to

control the work situation, low pay, dead-end job, un-supportive superiors, vague instructions, poor communication, role ambiguity, and excessive administrative duties. The individual characteristics include personality inclinations (tendency to react depressively, introversion, insecurity in dealing with others, being overly meticulous, perfectionism, compulsive behavior patterns, intolerance, impatience, inability to set limits, exaggerated idealism, low self-esteem, anxiety, dependency on the approval of others), ethnicity and individual history, passive coping strategies, underestimating environmental factors, and unrealistic expectations. Interpersonal relationships includes factors like focusing on the problems of customers and the frustrations/aggressions associated with them, chronicity of the problem, communication problems due to emotional reactions, dealing with pain and death, resisting help and intimacy of a relationship. Since a helping role figures prominently in this third factor, these problems might not be applied to other occupations unreservedly (15,16,117,118,120,122). BS is now diagnosed using mostly the Maslach burnout inventory (MBI) (116) and the Tedium Measure (117).

Upon careful consideration of the situation, the best approach might be stress management and burnout workshops aimed at preventing the victims' personal isolation by raising the self-esteem, fighting feelings of guilt and laying out a course of action. This approach would also be effective as secondary prevention. The advanced stages of BS may require psychotherapy, together with the aid of psychopharmaceuticals. In this connection, various forms of treatment are available, including behavioral therapy, supportive psychotherapy, group therapy, relaxation therapy and self-help groups (15,16,118,122–124).

At the personal level, career planning can be complemented by self-awareness and empathy training, as well as improving social skills, communication, understanding, tolerance, team spirit and cooperation. Regarding work and their environment, managers have the options of further education seminars, flexible time planning, changing occupational structures and roles, performance-based salary, autonomy, as well as management and training workshops. Additional preventive measures can be implemented, depending on the particular environment and hierarchies at the workplace (15,16,117,122,125).

Further details on BS are found in more in-depth publications (15,16,118,119,126–130).

RELATED SOMATOFORM DISORDERS

The high comorbidity of environment-related disorders and psychological, especially somatoform disorders,

strongly suggests a psychological origin of these problems (131–135). Furthermore, many do not see environment-related disorders as a new category in the sense of MCS or IEI, given that multiple-symptom disorders without a demonstrable organic cause have long been known under a variety of names (136). Göthe et al. (33) consider environment-related disorders a subclass of somatoform disorders. Several outbreaks of the so-called environmental somatization syndrome (ESS) showed a similar symptom pattern, mode of spread and sudden disappearance, differing only in their attribution and the culture where they occurred. Of all the somatoform disorders, the somatization disorder of DSM-IV and ICD 10 bear the greatest resemblance to MCS (137,138).

The somatization disorder is the most famous category of the somatoform disorders. Its main clinical signs are recurring multiple somatic symptoms which cannot be fully explained by organic illness or pathophysiological mechanisms (139,140). A history of numerous somatic symptoms persisting for several years is required for a positive diagnosis. Somatization disorder patients see themselves as seriously ill. Indeed, they often describe their health as more seriously impaired than do patients with chronic organic disorders. Typically, patients develop new symptoms during times of emotional stress.

Even though somatoform disorders number amongst the commonest psychological disorders, somatization disorder, with a prevalence of 0.4–0.5%, are rarely found due to the highly restrictive diagnostic criteria (141,142). Furthermore, somatoform disorders tend to be associated with a low educational level, low socio-economic status and a marked tendency to consult a physician and to seek inpatient admission at a hospital. Somatoform disorders also tend to show a chronic course with a remarkable diagnostic stability, misdiagnoses being rare (143,144). Also typical for somatoform disorders is their high comorbidity with depressive disorders (60–70%), anxiety disorders (30–50%) and personality disorders (60%) (145–147).

Considering only symptoms existing prior to onset of illness, 25% of MCS patients met the criteria of somatization disorder according to DSM-III R (vs. 0% of controls) (134). In a study on 50 patients with Environmental Hypersensitivity Disorder, 62% did not expect a cure (148). Black (149) remarked that many of his IEI patients would also meet the criteria for a diagnosis of hypochondria. An evaluation of the MMPI profiles of patients with MCS or CS (chemical sensitivity without a precise onset of illness) showed hysteria and hypochondria values typically associated with somatoform disorders (132,150). Davidoff (138) cited unfounded illness worries as the only psychopathological finding common to all patients. According to other authors,

environment-related disorders distinguish themselves from non-specific complaints reported with other illnesses, especially somatoform disorders, only in the attribution of cause to environmental toxins (151). A possible enhanced sensitivity towards chemical and physical stimuli notwithstanding, Schottenfeld and Cullen (152) also see an amplified perception of the development of an illusory conviction of being ill as the characteristic traits of MCS.

CONCLUSIONS

Table 1 shows a comparison of the various environmental syndromes. A categorical distinction of these syndromes is currently not possible due to the lack of precise knowledge on their etiology, pathology, pathophysiology, diagnosis, therapy, prognosis and prevention. It is therefore not surprising to read case reports where the same patient simultaneously or consecutively meets the criteria of the above discussed syndromes (17–21). All environment-related syndromes show a more or less obvious similarity with somatoform disorders. There are a number of overlapping explanations for environment-related syndromes:

1. They result from a hitherto poorly understood interaction of physical, chemical and/or biological environmental factors, individual susceptibility, psychological factors, as well as perception and coping mechanisms.
2. They are caused by distress resulting from or reinforced by cultural and social factors (e.g., change or loss of social context, work overload), which is expressed to a greater or lesser extent in form of an environment-related syndromes.
3. These syndromes are iatrogenic in origin and arise when the physician or health care worker, faced with a disorder of unclear causation, rather hastily assigns it a more or less likely term, not seldom also out of sheer convenience.

The complex diagnostic problems of environment-related syndromes lead many physicians and scientists to deny their existence, or else to classify them as psychosomatic-psychiatric disorders. This can have far-reaching and serious consequences for the patients who, 'dismissed' as psychiatric cases, become even more alienated and isolated. Due to the perceived ignorance and limited doctrines of traditional medicine, many dissatisfied patients turn to alternative methods of diagnosis and therapy, which often are ineffective, some downright harmful, and also burden the health care system financially.

In view of the considerable social and medical importance of these syndromes, a much urgently needed

Table 1 An attempt at comparing idiopathic environmental intolerance (IEI), multiple chemical sensitivity (MCS = chemical IEI), sick building syndrome (SBS), chronic fatigue syndrome (CFS), candida syndrome (CS), burnout syndrome (BS) and somatization disorders

	IEI	MCS IEI (chemical)	SBS	CFS	CS	BS	Somatization disorders	
Definition	Individual operational classification	Individual operational classification	Epidemiological operational classification	Individual operational classification	Individual operational classification	Individual operational classification	International operational definition	
Epidemiology	Not well known	Not well known	Mostly known	Not well known	Not well known	Not well known	4% of the general population	
Etiology	Multiple factors	Multiple factors	Multiple factors	Multiple factors	Individual conditions	Institutional, individual or interpersonal conditions	Multiple factors	
Potential trigger(s)	<ul style="list-style-type: none"> • Physical factors • Chemicals 	<ul style="list-style-type: none"> • Chemicals 	<ul style="list-style-type: none"> • Indoor factors 	<ul style="list-style-type: none"> • Micro-biological/immunological factors • Endocrinological factors • Neurological-psychiatric 	<ul style="list-style-type: none"> • Invasion by <i>Candida</i> • <i>Candida</i> infection • Gastrointestinal tract 	<ul style="list-style-type: none"> • Institutional, individual or interpersonal conditions 	<ul style="list-style-type: none"> • Heightened awareness of stress • Learned abnormal patient role • Defensive attitude 	
Most frequently affected organ systems	<ul style="list-style-type: none"> • Eyes • Airways • CNS • Musculoskeletal system • Gastrointestinal tract • Exclusion • Classification 	<ul style="list-style-type: none"> • Eyes • Airways • CNS • Musculoskeletal system • Gastrointestinal tract • Exclusion • Classification 	<ul style="list-style-type: none"> • Eyes • Airways • CNS • Skin 	<ul style="list-style-type: none"> • CNS • Musculoskeletal system 		<ul style="list-style-type: none"> • CNS • Musculoskeletal system • Gastrointestinal tract • Heart and circulatory system 	<ul style="list-style-type: none"> • Sociocultural • CNS • Musculoskeletal system • Gastrointestinal tract • Heart and circulatory system 	
Diagnosis			<ul style="list-style-type: none"> • Exclusion • Epidemiological classification 	<ul style="list-style-type: none"> • Exclusion • Classification 	<ul style="list-style-type: none"> • Exclusion • Classification 	<ul style="list-style-type: none"> • Exclusion • Classification • Maslach Burn-out Inventory • Tedium Measure • Symptom-dependent • Medication, drugs 	<ul style="list-style-type: none"> • Exclusion • Classification 	
Differential diagnosis	<ul style="list-style-type: none"> • Symptom-dependent • Medication, drugs 	<ul style="list-style-type: none"> • Symptom-dependent • Medication, drugs 	<ul style="list-style-type: none"> • Symptom-dependent • Medication, drugs 	<ul style="list-style-type: none"> • Symptom-dependent • Medication, drugs 	<ul style="list-style-type: none"> • Symptom-dependent 	<ul style="list-style-type: none"> • Antimycotic therapy • Diet poor in carbohydrates • Probiotic therapy 	<ul style="list-style-type: none"> • No specific therapy • Psychotherapy 	<ul style="list-style-type: none"> • Depressive disorders • Anxiety disorders
Therapy	<ul style="list-style-type: none"> • No specific therapy • Decrease or avoid exposure • Psychotherapy 	<ul style="list-style-type: none"> • No specific therapy • Decrease or avoid exposure • Psychotherapy 	<ul style="list-style-type: none"> • No specific therapy • Decrease or avoid exposure • Psychotherapy 	<ul style="list-style-type: none"> • No specific therapy • Psychotherapy 		<ul style="list-style-type: none"> • Antimycotic therapy • Diet poor in carbohydrates • Probiotic therapy 	<ul style="list-style-type: none"> • No specific therapy • Psychotherapy 	<ul style="list-style-type: none"> • Cognitive-behavioral therapy • Depth psychological therapy
Course of illness, prognosis	<ul style="list-style-type: none"> • Chronic course • Dissemination 	<ul style="list-style-type: none"> • Chronic course • Dissemination 	<ul style="list-style-type: none"> • Chronic course? • Dissemination? 	<ul style="list-style-type: none"> • Chronic course? • Spontaneous cure 	<ul style="list-style-type: none"> • Chronic course 	<ul style="list-style-type: none"> • Chronic course • Dissemination? 	<ul style="list-style-type: none"> • Chronic course or recurrence 	

comprehensive and thorough classification would properly address their complex clinical manifestations. Above all, currently employed but not yet validated diagnoses and therapies need to be evaluated scientifically, given that when choosing a doctor or therapist, the patient indirectly determines diagnosis and therapy. Furthermore, risk communication and coordination of patient management need to be optimized as soon as possible through effective cooperation between the health care system, institutions and insurances.

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