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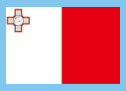

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World Journal of Dermatology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjdermatol@wjgnet.com
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Baishideng Publishing Group Co., Limited
Flat C, 23/F, Lucky Plaza,
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REVIEW

Stress involvement as trigger factor in different skin conditions

Liana Manolache, Dana Petrescu-Seceleanu

Liana Manolache, Dermatology Department, Dali Medical, 062079 Bucharest, Romania
Dana Petrescu-Seceleanu, Dermatology Department, Nicolae Kretzulescu Medical Center, 062079 Bucharest, Romania
Author contributions: Manolache L and Petrescu-Seceleanu D contributed equally to the manuscript.
Correspondence to: Liana Manolache, MD, PhD, Dermatology Department, Dali Medical, Str. Cetatea Histria nr. 12, sector 6, 062079 Bucharest, Romania. lianamanolache@yahoo.com
Telephone: +40-723-227427 Fax: +40-214-121980
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Abstract

Dermatological conditions are intimately related to stress. There was a great interest in this field in the last years. Stress could be involved as a trigger factor for a lot of cutaneous diseases: alopecia areata, psoriasis, vitiligo, lichen planus, acne, atopic dermatitis, urticaria. For other conditions: seborrheic dermatitis, hyperhydrosis, herpes, pemphigus, a.s.o, there are anecdotal notices. On the other hand, the skin disease itself could induce a secondary stress for the patient, influencing his quality of life. The stress *per se* is less important than the "perceived stress", the patient's perception of the stressful situation. This perception could be influenced by the psychological state of the patient. Anxiety, depression could change the perception of the event. It is important to take care of these aspects during the consultation. A good cooperation with psychiatrist or/and psychologist could improve the results, besides the specific therapy.

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Key words: Stress; Alopecia areata; Vitiligo; Psoriasis; Lichen planus; Acne; Urticarial; Atopic dermatitis

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INTRODUCTION

The state of health represents the balance between the mental, emotional, physical and relational areas. The stress means an abnormal or extreme physiological adjustment to the adverse effects of the environment. Selye defined stress and described the physiologic changes induced by stress, under the designation "general adaptation syndrome". About 80% of affections could be induced or aggravated by stress. The reaction to stress could be influenced by the genetics and also by someone's perception. The stressors could be environmental, behavioral or psychological[1]. The state of stress could be influenced by external factors (life events, social, work or natural environment) and individual factors (attitudes, traits, temperament, past experiences and needs) that are interconnected. The reaction depends on "how the person interprets or appraises (consciously or unconsciously) the significance of harmful, threatening or challenging event".

Stressful events could induce a psychosomatic disease, especially in some patients with high reactivity to stress. We can expect similar reactions of patients to major life events listed by Holmes and Rahe (death, serious illness-personal or of a family member, separations and divorces *etc*). But, there are other situations that can depend on the psychological traits of the patient, previous experiences, family models (reactions to exams, to different changes in life, to arguments). Alongside the effect of life stressful event, another factor that could influence the appearance and evolution of psychosomatic diseases is the psychological vulnerability of the patient experiencing the stress. Higher trait of anxiety could suggest this vulnerability.

Perceived stress could be more important and with a greater effect than the stressful event itself. The reaction of the individual is an attempt to restore the balance and depends on the coping abilities. Persons with high stress resistance are characterized by a control on the events and life situations, acceptance of the responsibility of the facts that are happening. They are involved in everything they are doing and they accept the changes as natural. The ability of patients to cope with stress could be reduced by alexythimia (incapacity to verbally express the emotions), insecure attachment and poor social support[2-4]. Social programs including stress management and psychological support are important in the achievement of coping abilities[5].

Even there are previous observations of stress relation with different dermatoses, first mentions of psychosomatic dermatology are from the early 80's, when Cermak and Panconesi described the connection between "psyche and skin diseases"[6,7].

Skin responds to different types of stressful stimuli and psychologic states. Stress intervenes through the hypothalamic-pituitary-adrenal (HPA) axis with the release of neuromediators from the nerve endings and dermal cells (neuropeptides, neurotrophins, lymphokines). There are connections among endocrine-nervous and immune systems. Stress has been reported to cause decreased natural killer cell cytotoxicity, depressed mitogenic responses in lymphocytes, increased IgA levels, enhanced neutrophil phagocytosis and activation of interferon synthesis in lymphocytes[8].

Corticotropin-releasing hormone (CRH) coordinates the systemic stress response *via* hypothalamic-pituitary-adrenal axis activation with subsequent modulation of the inflammatory response. Stress can affect expression of immune-mediated inflammatory diseases, associated with HPA axis abnormalities. HPA axis components including CRH and its receptors (CRH-R) exist in the skin and exhibit differential expression according to cell type, physiological fluctuations and disease states. This confirms a local functioning cutaneous HPA-like system. Peripheral CRH may exhibit proinflammatory effects. CRH may influence mast cell activation, modulation of immune cells and angiogenesis[9].

Mast cells play an important role closely linked to the sensory nerves in the skin. During psychological stress there is a release of neuromediators, CRH and alfa-MSH (melanocyte-stimulating hormone) that are activating mast cells. Mast cells' mediators (histamine, tryptase and NGF-nerve growth factor) can stimulate the neuropeptide-containing C fibers, increasing the inflammation. Mast cells are releasing pro-inflammatory cytokines and chemokines[10].

Psychological stress has a negative impact on cutaneous permeability barrier function, mediated by increased endogenous glucocorticoids[11,12]. There is an inhibition of epidermal lipid synthesis[12]. Psychological stress could also compromise the antimicrobial defense, also by glucocorticoid-dependent mechanisms[13].

The role of stressful events in psoriasis, alopecia areata, atopic dermatitis, pruritus and urticaria seems to be apparently clearer. The role of stressful events in vitiligo, lichen planus, acne, rosacea, pemphigus and seborrhoeic dermatitis is either controversial or insufficiently explored[1,14-16].

ALOPECIA AREATA

Hair is very important in our lives, even since childhood, so hair loss could affect both self-image and social relations. The aetiopathogenesis of alopecia areata is complex, and includes genetic factors, autoimmune processes, infectious factors and psychological factors (stress and personality characteristics of patients).

First observations are dating from early "60's when alopecia areata was related to mental stress[17,18]. It took about 15 years to come again to the idea of "alopecia areata and stressful events"[19] or correlating hair loss in children to underlying emotional disturbance[20]. Patients with alopecia areata are considered by some authors to lack symbolic or language schemes of representation for experiences of separation and loss, which affects personality and creates a devoid-of-affect impression. Alopecia areata patients have high rates of alexithymia and avoidant behavior that could reduce the ability to cope with stress[1,21,22]. In 1991, there is a case-control study on 92 Saudi patients associating atopy and psychological stress to alopecia areata[23].

There are different opinions regarding the involvement of stress in alopecia areata. Some believe that general events could appear in up to 80% of cases with alopecia areata, with 62% stating this as a serious event[24]. Other studies found stress involvement as precipitating or aggravating factor in 55% to 75% of cases (compared to 20% in controls)[25]. On the other hand, Tan *et al*[26] found that stressful events preceded hair loss in only 9.8% of 132 alopecia areata patients. Van der Steen *et al*[27]. did not correlate the pathogenesis of alopecia areata with emotional stress. It seems that stress in alopecia areata is not recent (*i.e.*, during the past year), the "aetiology" being much more insidious. Old stressful situations are reported more often, revealing a chronic stress[28]. A case-control study on 90 patients reported total lifetime and early childhood traumatic disease, alopecia areata patients having a higher score of the global impact to their traumatic experiences than controls[29].

Some studies mention the importance of perceived stress, which is sometimes even more important than the stressful situation itself for both the first episode and recurrence[30,31]. Gupta cited a study by Andersen, in which only 23% of subjects had recent stresses that occurred less than 3 mo before disease onset[32]. Gupta *et al*[33] described alopecia areata patients in their study as having high reactivity to stress; these patients also had higher scores for depression. Picardi *et al*[3] did not find significant differences between the same two groups when comparing the total number of stressful events

and the number of undesirable or major events (21 cases studied). Moreover, the control group had a greater number of uncontrollable events. The authors support the idea of the influence of personality characteristics (alexithymia, avoidance of attachment relationships) or poor social support on individual susceptibility to stressful situations. As for children and adolescents are even fewer reports regarding stress, starting from no correlation with stress (to involvement of stressful events in up to 80% of children)[34].

There are reports that alopecia areata pediatric patients experienced more stressful events[35,36]. In studies regarding alopecia areata in children and teenagers stress seemed to be a precipitating factor in 9.5% of cases (up to 3 mo prior to onset of disease)[37], or even in 58% of cases[38]. Liakopoulou *et al*[39] correlate the alopecia areata in children with the lack of positive events during the time before the onset (33 cases). There are other studies[40] that had found no significant difference between the mean number of positive or negative life events in children with alopecia areata (12 cases compared to a normative sample). The types of events noticed by children with alopecia areata were mostly related to school (beginning school or kindergarten, exams at the end of gymnasium, change of class or school, problems with school-mates or teachers, too many classes or homework, children feeling over-solicited)[38]. Other data[37] had found similar types of events involved before the onset of alopecia areata in children: family disputes, starting school, parent's divorce, operation, but also different kinds (birth of a sibling, commencement of speech therapy). The study of Andreoli[35] on 180 children and teenagers has proposed as potential stressful events: separations (from people, pets, habits, things or familiar environment) in 37% of cases, relational problems (in family, school, with friends) in 32% of cases, but also the difficulties for the child to fulfill the parents' expectations (especially in school activity) in 24% of cases.

PSORIASIS

Psoriasis is a chronic inflammatory with a prevalence of 2% in general European population and even higher in children (4% in children under 16 years old)[41]. Even the impact on the patient's and family's life is important, only a few studies are searching for the presence of stress as potential triggering factor.

The aetiopathogenesis is complex, including genetic and environmental factors. Among risk factors, stressful life events[42-45] seem to play important roles. In 1980, Fava[46] noticed that patients with psoriasis were exposed to stressful life situations before onset significantly more than those with fungal infections. In Burkhart *et al*[14] review, the role of stressful events in psoriasis seems to be clear for both onset (42%-72%) and relapses (80%). But, there are other studies that found no difference comparing psoriatic patients to controls regarding the mean number of recently experienced life events, the number of undesirable, uncontrollable or major events[4,47]. In a prospective cohort study[48] no association between psoriasis and antecedents of stress was revealed. Despite the constant interest for stress involvement in psoriasis, case-control studies were made only during last years and only a few were using a type of questionnaire to investigate the presence of life events[4,47,49]. Most of papers are presenting self-reported situations.

There are different data in the literature. Results regarding stress involvement are starting from values of 6.9% (precipitating)[50], 35% (for onset)[51], 45%-50% (for onset/recurrence)[52-54], up to 60%-72% (for onset[55,56] or exacerbation[51,56-58]). "Incubation" period differs from 15 d (honeymoon)[56], to one month before the onset/exacerbation[52], three months[55], or six months[52]. Compared to controls, patients with psoriasis reported more stressful events during the last 12 mo[49]. There is a comparative study presenting stress induced exacerbations in children (50.4%) and adults (42.7%)[59].

There are studies that found no significant differences between patients and controls regarding the total number of stressful events, the number of undesirable, uncontrollable and major adverse events, or no correlation between the severity of stress and the moment of onset or exacerbation of psoriasis[4,60]. A prospective study, but on a small sample (9 women) does not support the idea of psoriasis worsening by stress[61]. Stress was associated with psoriasis only for patients experiencing four or more stressful events in the preceding year[14]. Patients with psoriasis had a very high level of perceived stress and a deeply altered quality of life[62]. Patients' beliefs of stress involvement range from 37% to 78%[63]. Daily stressors influence disease outcome in patients with psoriasis by affecting cortisol levels at moments of high stress. Furthermore, patients with persistently high levels of stressors seem to have a specific psychophysiological profile of lowered cortisol levels and may be particularly vulnerable to the influence of stressors on their psoriasis[64].

Family stress influences the psychological well being more than other types of daily stress events in patients with psoriasis[65]. Family matters were mentioned by 42.7% of psoriatic patients, statistically significant compared with controls ($P < 0.0001$). In 35% of psoriatic cases, "the stressful event" was represented by the illness/death of someone dear[54].

An interesting study[66] compared the differences in stressful situations described by psoriatic patients during peace and war time. During peace periods there were evoked, as in our study, death of a family member, own disease or serious disease of a family member, but also problems with children education, divorce or marriage. War time stressful situations were different: killing/wounding some member of family or close to person, wounding inquiring person, separation from wife/children, loosing of property or soldiering in the army[67].

There are studies mentioning that up to one third of patients could have the very first lesions even since childhood[41,67], which can increase the psychological distress

during the formative years. Negative traumatic experiences could influence the onset of psoriasis both in early childhood and adulthood[68].

There is a lack of studies in pediatric dermatology regarding the subject of stress involvement. There are reports of stress[67,69] as trigger in psoriasis among other factors such infections[67,69,70], summertime[69] or trauma[69]. Most of the data mention inflammatory focus as the most frequently trigger in childhood psoriasis[70,71]. Negative traumatic experiences during childhood seem to be present in psoriatic patients, but there is no correlation between the severity of the disease and traumatic experiences[68]. Seyhan *et al*[71] found the presence of emotional stress in more than half of a group of 61 cases. A study[59] on 223 cases reports that psoriatic lesions could be exacerbated by stress (50%), but also by upper respiratory tract infection (28%) and trauma (49.6%). In a very recent case-control study, children with psoriasis mentioned more often than controls the presence of stressful life events in the year preceding the disease and also environmental tobacco smoke exposure at home[72]. But, there are also reports of patients not aware of any role of infections, injury or stress as precipitating factors of psoriasis[73].

VITILIGO

With a 3000 year history, vitiligo is one of the important stigmatizing skin conditions. The importance of stressful events, including the number of these, before the onset has been described in several case-control studies[74,75]. Stress is reported before onset in more than half, up to 65% of patients[74,76,77]. Patients with vitiligo had a significant number of stressful events in the year preceding the onset of the lesions, compared to controls[78]. But, there are other studies with no differences between vitiligo patients and controls, comparing the number of stressful events[2,74]. Women seem to be more sensitive to stress, mentioning more stressful events than controls[74]. Vitiligo patients reported more than controls the exposure to three or more uncontrollable events, suggesting that alexithymia, insecure attachments and poor social support could reduce the ability to cope with stress, increasing the susceptibility to vitiligo[2].

Potential stressful situations reported in other vitiligo studies were marital or financial problems[75], loss of loved ones (*e.g.*, death, separation), illnesses and changes in eating or sleeping habits[75]. In a study by Silvan, 40% of vitiligo patients experienced the death of a close friend or family member. In comparison, 25% of vitiligo patients experienced loss in a study by Papadopoulos *et al*[75]; loss in this case meaning relocation, or the loss of friends, family, or familiar surroundings[75,79]. Patients with vitiligo often have different perceptions of the etiology of their disease. They thought that both stress (30%-60% of cases) and genetic background (2432%) are involved[77,80]. There are few reports of the psychosocial impact of vitiligo on children and adolescents although vitiligo can have a serious impact on their lives. This ranges from vitiligo having no correlation with stress to involvement of stressful events in about 50% of cases[70,81]. Psychological vulnerability can also influence the onset and evolution of psychosomatic dermatoses, alongside the presence of stressful events. A recent study[82] on the temperament of children with vitiligo revealed that these children score high on the "harm avoidance" scale, meaning that compared to their healthy siblings, children with vitiligo seem to have a greater fear of strangers and have a heightened response to any changes in a close relative. Age, change of location, and situational or environmental alterations can also be predictors of stress. About half of vitiligo vulgaris patients have onset of their illness during childhood, which can increase psychological distress during the formative years[83]. On the other hand, in the prepubertal period, children are not focused yet on their physical appearance, so an early onset could also act as a "protective factor", enabling the child to develop compensatory mechanisms of coping with disease and ways to strengthen self-esteem[84]. Periods of adjustment to new conditions, such as the beginning of education (school or kindergarten), being an only child, or having separated parents (particularly in boys) could be considered special situations in which children with vitiligo need more support and require the intervention of families, teachers and doctors[81].

LICHEN PLANUS

Lichen planus is a dermatological condition that could appear in 0.38% to 6%[85,86] of outpatients, mostly over 45 years old[87]. There are different opinions regarding the etio-pathogenesis of lichen planus, some of them correlating stress involvement with the onset/extension of the disease. There are not so many papers studying the presumed role of stress in lichen planus patients, and most of them are referring to oral lesions only. Stress, alongside spicy food, poor oral hygiene could precipitate or aggravate oral lichen planus[88,89]. Burkhart *et al*[14] made a correlation between stress and oral lichen planus, a stressful situation before the onset being reported in 51% of cases, but there was no control group included[90], but with no control match. There is another study on 46 patients with lichen planus that revealed with stress involvement in 67% of cases, compared to 21% in controls[91]. In a study of 55 cases, Mansur[92] described stressful events in almost 90% of patients with cutaneous lichen planus. As for oral lichen planus, there is a mention of stress presence in up to 90% of 30 cases (case-control study)[93]. On the other hand, there are studies that did not observe more stressful life events in oral lichen planus patients compared with controls[94,95]. Patients with lichen planus could have higher levels of salivary cortisol than controls, revealing a correlation with the level of stress[93,96,97]. A study on oral lichen planus has not found any difference between patients (30) and controls regarding the salivary cortisol level[94]. Family problems seem to be

more important as stressful events in patients' lives[91,92]. Lundqvist *et al*[98] found moderately increased perceived stress in 17% of lichen planus cases (erosive lesions: oral and genital) compared with 8% in controls. Thirteen per cent of cases reported high stress level compared to 3% in controls. Symptoms from both genital and oral area interfered with daily life, work and social life/spare, higher scores of perceived stress influencing this interference.

ACNE

During the last years it was a debate regarding the importance of stress involvement in acne evolution. Some studies reveal the presence of perceived stress. Patients' beliefs should be taken in consideration, they consider stress as aggravating factor.

The skin, especially the pilo-sebaceous unit, could be seen as an endocrine organ, being a target for hormones, synthesizing hormonal substances and expressing diverse hormone receptors. Recently, neurogenic factors were considered involved in the acne pathogenesis. The effects of neuropeptides on the morphology of sebaceous gland were studied. The substance P that could be increased in stressful situations induces the proliferation and differentiation at the sebaceous gland[99,100]. At the level of acne-involved skin there is an over-expression of CRH system, activating inflammatory and immunological processes with an exacerbation of acne lesion during stressful situations[101].

There are studies suggesting stress as an important factor in the pathogenesis of acne, up to 90% of cases[102-105]. Both girls and boys are mentioning mental stress, the score of stress increasing with the severity of acne[106]. Teenagers from Singapore were evaluated in periods of intense stress (before examinations) and low stress (summer holiday). There were no differences in the secretion of sebum. There was a correlation between the level of stress and the severity of lesions, suggesting other mechanisms besides the seborrhea[107]. More important was the perception of stress and patient's belief related to the possible cause. Stress is seen as a precipitating and aggravating factor for acne lesions, besides hot weather, excessive sweat, poor hygiene, smoking, alcohol intake or chocolate[108-113]. Patients with high levels of stress and with the tendency to develop dysmorphophobia have to be approached in a complex manner together with psychiatrists and psychologists[114]. Stress involvement in the precipitation and exacerbation of acne is still a dilemma, some studies denying this hypothesis[115]. The debate is open, future studies will certify or deny the observations and patients' beliefs.

ATOPIC DERMATITIS

Atopic dermatitis is a complex disease traditionally involving interaction of genetic, environmental, and immunologic factors. First observations of the correlation of life situations, emotions and atopic dermatitis are coming from 1949[116]. In 1976, emotional stress had to be considered in the evaluation of children with atopic dermatitis[117]. Then, in 1986, data from 19 countries from Europe and North America include psychic stress among decisive factors[118].

Stress is considered as a triggering factor, besides exercise, climatologic factors, sweating, irritants, aeroallergens, food, microbial organisms[119-121]. Patients with atopic dermatitis have a hyporesponsive hypothalamo-pituitary-adrenal axis, with a concurrent over reactivity of sympathetic adrenomedullary system[121-124]. Psychological stress has different immunologic effects in patients with atopic dermatitis including a shift in immunity toward a T helper type 2 cell/allergic response[125,126]. Neuropeptides released in the skin may also mediate neurogenic inflammation, including mast cell degranulation[127,128]. Suckling reduces the plasma levels of SP, VIP and NGF[129]. There is a correlation between self-reported stress during pregnancy and maternal NGF levels, important in predicting children with a risk of atopic dermatitis[130]. Patients with atopic dermatitis showed increased IgE levels 24 h after Trier Social Stress Test (free speech and mental arithmetic tasks in front of an audience)[131]. High technology causes stress that could aggravate the atopic dermatitis symptoms. Playing video games and computer-induced stress increase the plasma levels of substance P and VIP, specifically in patients with atopic dermatitis[132]. Writing mail on a mobile phone enhance the plasma NGF and allergic symptoms[131,133]. Laughter caused by viewing a comic video reduces the plasma NGF, neurotrophin-3 and allergic responses[134]. Humorous films could be useful in the treatment of night-time wakening that is often in patients with atopic dermatitis. These patients have elevated salivary ghrelin levels at 2 am, ghrelin being involved in growth hormone secretion, regulation of appetite, anxiety, night-time wakening and stress[135]. Stress impairs skin barrier function, both the barrier homeostatis and stratum corneum integrity[1,127,128]. Teenagers with atopic dermatitis had reported mental distress correlated with their symptoms[136]. Divorce/separation of the parents, severe disease or death of a family member could influence the risk of developing atopic eczema in children[137]. Family environment is important predictor of symptom severity[138]. Stressful social interactions with more negative communication patterns could add to the patients' level of stress aggravating the course of atopic dermatitis[139]. Stress caused by a natural disaster is also influencing the symptoms[140]. Stress-induced exacerbations make psychosomatic counseling recommended. "Eczema schools" educational programs are helpful[141].

URTICARIA

Stressful life events seem to be important as precipitating and aggravating factor in chronic urticaria[142,143]. 16% of the patients in the chronic urticaria group reported stressful events within 1 year preceding onset or exacerbation of skin disease[144]. In the 6 mo preceding disease

onset, patients with chronic idiopathic urticaria had significantly more life events with a higher subjective impact of them[145,146]. More than 37% of chronic urticaria patients reported stress as aggravating factor[147,148]. In the chronic urticaria group, the most common stressful life event seen was death of a close family member. Family disputes, financial problems, sexual problems, illness of a family member, getting married or engaged, trouble at work could be also be involved[147]. Posttraumatic stress was associated with chronic idiopathic urticaria through alexithymia and defensive attitude[149,150]. Perceived stress is also important in the evolution of chronic urticaria[151,152]. There are other reports that do not correlate stress with the course of the disorder (*e.g.*, psychosocial stress test does not alter the dermographic reaction)[152,153]. Insomnia could be an important predisposing factor for urticaria[145]. Good ego-function, coping strategies and family support were associated with decreased frequency of urticaria[147]. Relaxation therapies, stress management could be useful in the complex approach of chronic urticaria patients[145,154,155]. Skin tests in allergic patients could be significantly improved with autogenic training and relaxation[156].

SEBORRHEIC DERMATITIS AND OTHER DISEASES

The role of stressful events in seborrheic dermatitis is controversial or insufficiently studied[14]. Mental stress can influence the disease, causing flare-ups and being the main triggering factor[157-159]. Stress suggests a poor prognosis[159]. Studies on musicians reveal an important incidence of hyperhydrosis, lichen planus, psoriasis, seborrheic dermatitis and urticaria, because of the emotional factor involved[160]. Overtiredness and mental stress could induce more frequent relapse for both oral and genital herpes[161,162]. Stressful life events can worsen or trigger pemphigus[163].

CONCLUSION

Stress is a very important factor to be taken in consideration as precipitating or aggravating factor in different skin conditions. We should consider both stressful life event itself and the impact on patients' life (perceived stress). Psychosomatic approach is recommended, involving stress management, relaxation sessions, educational programs and psychiatric consultations.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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Books

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Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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