Environmental factors and allergic diseases

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Abstract

An objective of this article is a review of contemporary knowledge on various environmental factors, that influence prevalence and course of allergic diseases, like asthma, allergic rhinitis, atopic dermatitis and also contact dermatitis. Surrounding climate may directly influence each patient, but also determines type of flora and fauna within particular geographical regions and thus affects sources of airborne and food allergens. Epidemiological studies suggest that there is a strong relationship between air pollution and development and exacerbation of asthma and other allergic diseases – main attention has been concentrated on gaseous materials such as ozone (O3) and nitrogen dioxide (NO2), as well as particulate matter (PM), generated by car traffic and industry. Diesel exhaust particulate (DEP) has the ability to bind proteins and may serve as a potential carrier of allergens, penetrating deep into respiratory tract. Among the most extensively studied environmental factors influencing allergy are airborne allergens: dust mites, pollens, fungi and animal dander. Foods may elicit both true IgE-mediated allergy and also various non-immunological reactions, associated with direct release of mediators or toxic activity. It has been estimated, that over 85 000 chemicals are recognized in the human environment and they may act as contact allergens or irritants, causing allergic or non-allergic contact dermatitis. Among them metals, fragrances, preservatives, botanicals and paraphenylenediamine are considered as the most significant. Infections have always been associated with etiopathogenesis of allergic diseases and they may contribute to exacerbation of their course.

Key words

environment, atopic dermatitis, contact allergy

INTRODUCTION AND OBJECTIVE

Allergic reactions are considered as multifactorial, heterogeneous disorders caused by an interaction of environmental and genetic factors and can express themselves in many different organs (typical allergic symptoms include asthma, rhinoconjunctivitis, gastrointestinal symptoms, and skin lesions), and in any age group. According to the European Academy of Allergology and Clinical Immunology (EAACI) revised nomenclature for allergy [1], allergic hypersensitivity (with defined or strongly suspected immunological mechanism) may be classified either as IgE-mediated or not-IgE mediated, the latter being associated with specific T-cell response, as in contact dermatitis. IgE-mediated mechanism is associated with atopy, defined as a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms, such as asthma, rhinoconjunctivitis, or eczema/dermatitis.

Allergic (atopic) diseases result from an interaction between individual genetic susceptibility and exposure to environmental factors. According to twin studies, the genetic contribution to allergic disease has been estimated as more than 50%, with heritability estimates ranging from 36-79% [2, 3, 4]. Due to probable changes in the environment, an increase in the prevalence of allergies in the past decades has been observed. Environmental factors, in combination with genetic predisposition of a patient may contribute to the development of so-called extrinsic forms of asthma or atopic dermatitis, which are accompanied by sensitization to environmental factors and the presence of antigen-specific serum IgE [2, 3, 4, 5].

On the other hand, genetics of contact allergy is still only partly understood despite decades of research, which might be due to inadequately defined phenotypes used in the past. According to recent literature data, susceptibility to contact allergy may be influenced by genetically determined alterations in the production of pro- and anti-inflammatory cytokines, influenced by variable haplents, present in the surrounding environment, including the occupational milieu [6].

The objective of this study was to review selected environmental factors, characterized by the most significant influence on the prevalence and course of various allergic diseases: asthma, allergic rhinitis, atopic dermatitis and also contact dermatitis.

Climate. Climatic conditions seem to have a significant impact on allergic patients, especially those suffering from atopic dermatitis. Climate may directly influence each organism, but on the other hand, determines the model of flora and fauna within particular geographical regions and thus determines the sources of airborne and food allergens. It is well-known that increased temperature increases sweating, causes high water loss, and therefore skin dryness and pruritus. On the other hand, UV radiation causes destruction of microorganisms colonizing the skin and some of them may act as superantigens, contributing to the exacerbation skin lesions. The beneficial effects of sunlight and wind at the seaside have been used for centuries to treat skin diseases as ‘thalassotherapy’ [7, 8, 9, 10].
Air pollution. For years, urban air pollution has been a matter of research as an important extrinsic, environmental etiologic agent. Attention has been concentrated mainly on gaseous materials, such as ozone \((\text{O}_3)\) and nitrogen dioxide \((\text{NO}_2)\), as well as particulate matter \((\text{PM})\), generated by car traffic and industry [11]. Epidemiological studies suggest a strong relationship between air pollution and both development and exacerbation of asthma and other allergic diseases. Animal experiments show that IgE-mediated hypersensitivity to ovalbumin develops more efficiently when the animals were exposed simultaneously to diesel exhaust particles \((\text{DEP})\) or \(\text{O}_3\). It is suggested that air pollutants may intensify allergic reactions by modifying the epithelium, influencing immunity, and increasing the allergenicity of particular antigens (atopens). Recent literature data suggests that allergens and pollutants are effective not only additively, but may also augment allergic reaction [11, 12].

\(\text{O}_3\) is the main component of photochemical oxidants and so-called ‘summer smog’, and might account for up to 90% of total oxidant levels in cities of the Mediterranean area or California. Even up to 60% of inhaled \(\text{O}_3\) is absorbed within the upper airways, and the rest within the lower levels of the respiratory tract. Increased air levels of \(\text{O}_3\) and \(\text{NO}_2\) have been associated with increased respiratory morbidity and with hospital admissions for asthma in the case of both children and adults [11, 12, 13]. The most significant source of outdoor \(\text{NO}_2\) is automobile exhaust. Similar to \(\text{O}_3\), \(\text{NO}_2\) is an oxidant pollutant, although it is less chemically reactive and thus probably less potent. The major component of urban air pollution is \(\text{PM}\) and it is considered as the most serious air pollution problem in cities and towns, particularly being associated with various adverse health effects. \(\text{PM}\) is a mixture of solid and liquid particles of different origin, including pollen grains and mold spores.

Diesel exhaust particulate \((\text{DEP})\) accounts for most of the airborne \(\text{PM}\) (up to 90%) in the atmosphere of the world’s largest cities. Acute exposure to diesel exhaust may cause irritation of the nose and eyes, headache, lung function disturbances, respiratory changes, fatigue and nausea, while chronic exposure is usually associated with chronic cough, sputum production and lung function decline. \(\text{DEP}\) are characterized by both adjuvant activity for sensitization against common allergens and enhancing effects on allergic symptoms in sensitized patients. Up to 30% of inhaled \(\text{DEP}\) can be deposited in the alveolar region of the respiratory tract, and a large proportion is phagocytosed by alveolar macrophages. Literature data suggests the ability of \(\text{DEP}\) to bind proteins (for example, house dust mite – \(\text{HDM}\) allergens), which is why it may be considered as a potential carrier of allergens. It is particularly important that the majority of these particles are small enough to penetrate deep into the respiratory tree and provoke allergic symptoms [14, 15, 16, 17].

Airborne allergens. These are among the most extensively studied environmental factors regarding the source of potential risk for sensitization and manifestation of atopy, in consideration of both the airways and skin. Cross-sectional studies regarding children and adults strongly suggest that there is a close association between allergen exposure and sensitization to specific allergens. Longitudinal studies, such as the MAS study conducted in Germany, have demonstrated that during the first years of life there is a dose–response relationship between indoor allergen exposure to \(\text{HDM}\) and cat allergens and the risk of further sensitization to cat and \(\text{HDM}\), respectively [18].

Airborne allergens may both elicit or exacerbate allergic diseases – for example, the induction of atopic dermatitis by airborne allergens has been verified in various studies [19, 20]. Airborne allergens include perennial allergens \((\text{HDM}, \text{cockroach}, \text{animal dander})\) and seasonal allergens \((\text{pollens, molds})\). \(\text{HDM}\) allergens are among the most precisely analyzed, and current studies show that hypersensitivity to \(\text{HDM}\) applies to 5% of all the Western European population. The main source of \(\text{HDM}\) allergens are their excrements (diameter of about 25 microns). Such a small volume of excretions enables it to float easily in the air or to lie in a bed, pillows, mattresses and carpets. Another important origin of perennial allergens are cockroaches, both American \((\text{Periplaneta americana})\) and German \((\text{Blatella germanica})\) species. The development of hypersensitivity is associated with the presence of their droppings and secretions in house dust. Their influence on the exacerbation of atopic dermatitis has not been fully elucidated; however, there are reports of a high incidence of positive reactions of patch tests in children with atopic dermatitis, which could indicate that next to \(\text{HDM}\), cockroaches may contribute to exacerbations of skin lesions in susceptible individuals [21, 22, 23, 24, 25].

Domestic pets (particularly dogs and cats) and their hairs, skin, saliva and urine are considered also an important source of allergens. Dander of farm animals, such as horses and cows, is of much less importance but may be significant from the occupational or recreational point of view. Some atopic patients also potentially react to feathers, although in some cases it may not be clear whether hypersensitivity reactions are associated with the feathers themselves, or from the mixture of allergens from \(\text{HDM}\) and moulds inhabiting a pillowcase [22].

Exacerbation of symptoms in allergic patients during spring, summer or autumn drew attention to flowering plants and their pollens as an important seasonal source of allergens. Plants pollinated by insects produce relatively small amounts of pollen and only close contact with them causes symptoms. The most significant from the standpoint of airborne allergy are anemophilous plants producing enormous amounts of pollen within a short period of time. Pollen grains, characterized by a diameter of 20–60 microns, may be transmitted over long distances [26, 27]. Throughout the year, there are 4 major periods of pollination, including certain plant species. The first period (January – mid-May) is associated with tree pollination – mainly by hazel, alder and birch. The second period lasts from mid-May – early June, and is associated with vigorously pollinating trees, such as fir, beech, and willow, which is the most potent antigen. In Europe, coniferous tree pollen is not considered as substantial, but in Japan cedar pollen allergens are considered as an important cause of atopic dermatitis and asthma exacerbations. During the third period (early June – mid-July), grass pollen predominates and is regarded as the most common cause of pollinosis worldwide. In Central Europe, the most prevalent grasses include timothy grass, ryegrass, meadow fescue and velvet grass. The fourth period (mid-July to late September) is associated with increased pollination of weeds, with the principal allergic species including \textit{Artemisia} and \textit{Chenopodium} [28, 29, 30, 31].

Another possible mischievousness of airborne allergens or substances should be considered in terms of hypersensitivity is
Food allergens. According to the World Health Organization, food allergy concerns 4-10% of children (including 6-8% and 3-5%, respectively, of infants and children up to the age of 8 years) and 2-4% of adults. EAACI defines food hypersensitivity as a reaction provoked by exposure to food in amounts tolerated by the majority of the population, with an objective and reproducible symptoms. When immunologic mechanisms have been demonstrated (for example, the role of IgE is confirmed), the appropriate term is food allergy. All other reactions, previously sometimes referred to as 'food intolerance', should be referred to as non-allergic food hypersensitivity. Severe, generalized allergic reactions to food can be classified as anaphylaxis [34, 35, 36, 37]. In accordance with other allergic (atopic) conditions, food allergy may be familial. Genetic predisposition to developing food allergy has been previously demonstrated in studies involving twins. In this case, the concordance rate for inheriting the predisposition to develop hypersensitivity to peanut allergens among monozygotic twins was 64.3%, while in dizygotic twins it was evaluated as approximately 6.8%. Literature data suggests that the risk of inheriting a predisposition to peanut allergy in twins is similar to the heritability of bronchial asthma, allergic rhinitis, or atopic dermatitis [37, 38, 39].

Non-allergic food hypersensitivity may be associated with food itself, but also with chemical substances added to food to improve its organoleptic properties. Miscellaneous symptoms may occur in the course of pancreatic disease (deficiency of digestive enzymes – lipase, disaccharidases), liver problems (abnormal production of bile components or enzymatic proteins), or congenital lactase deficiency. So-called pseudoallergic reactions to various dietary products may appear due to the high content of biogenic amines in them (mainly histamine, tyramine, serotonin). Foods including these mediators (chocolate, fish, strawberries, bananas, citrus fruits, spinach, ripe cheeses, some sausages and wines) may elicit response that mimics IgE-mediated reaction, but allergological diagnostics fail to prove the involvement of IgE.

Also widely analyzed are hypersensitivity reactions to various food preservatives (benzoic acid), azo dyes (tartrazine – E102, erythrosine – E127, sunset yellow – E110, brilliant black – E151), as well as substances which improve taste (monosodium glutamate – E621, aspartame – E951). It is worth emphasizing that because of the similarity of the chemical structure of the above substances to aspirin, they may increase production of sulfidoleukotrienes and cause similar adverse symptoms as in acetylsalicylic acid intolerance (urticaria, angioedema). It has also been demonstrated, that antioxidants (aspartame – E951, benzoic acid – E210, butylated hydroxyanisole – BHA – E320, butylated hydroxytoluene – BHT – E321) and food dyes may cause direct mast cell degranulation with subsequent release of large amounts of histamine. On the other hand, some other food contents, such as aflatoxins (peanuts, almonds, corn), pesticides (fruits, vegetables) or heavy metals (fish, meat) may be associated with symptoms of food intolerance, resulting from the toxic effects on the gastrointestinal tract or the whole system, with symptoms like weakness, malaise, or neurological disturbances [40, 41].

Patients sensitized to pollen allergens may present cross-reactivity with certain foods [42]. It has been observed that adolescent or adult patients suffering from pollinosis associated with birch pollen allergens, in 50%-70% also show immediate symptoms upon ingestion of birch pollen-related fruit and vegetables [43]. Various foods have been identified as birch pollen-related, including particularly plant families such as Rosaceae, Solanaceae, and Umbelliferae. Among these, apple, hazelnut, carrot, and celery most often induce symptoms associated with oral allergy syndrome, urticaria, angioedema, rhinoconjunctivitis, asthma, or even anaphylactic shock [44, 45]. It is well-known that the birch pollen major allergen (Bet v1) is mainly involved in the development of cross-reactive IgE antibodies to apple, celery, and hazelnut. On the other hand, protein profilin Bet v2 (panallergen – responsible for many IgE cross-reactions even between unrelated pollen and plant food allergen sources) and protein Bet v5 have been identified as cross-reactive minor birch pollen allergens. High levels of antigen-specific IgE to birch pollen and Bet v1/Bet v2 have been detected in the sera of patients suffering from atopic dermatitis [46, 47, 48].
With regards to bacterial infections, recent observations suggest also the potential significance of atypical bacteria: *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. It is suspected, that these microbes may enhance inflammation and simultaneously increase sensitivity to stimulation by other factors, causing lack of asthma control and contributing to its severe course. Such patients respond well to macrolides, but the true action of these drugs (antibacterial, anti-inflammatory) has not yet been elucidated [55, 56].

In case of patients suffering from atopic dermatitis, the role of bacteria and yeasts has long been a matter of research. It is well known that *Staphylococcus aureus* may cause severe exacerbation of eczematous skin lesions, mainly by releasing exotoxins which act as superantigens that stimulate the activation of T-cell and antigen presenting cells, as well as epidermal cells (keratinocytes) [57, 58]. In some cases, IgE-dependent sensitization to bacterial enterotoxins is also observed. In addition, *Staphylococcus aureus* increases the expression of cutaneous lymphocyte-associated antigen (CLA) and determines the development of resistance to glucocorticoids [59, 60].

Recently, attention has also been drawn towards opportunistic yeast species *Malassezia* as a factor involved in the development and exacerbation of skin lesions in atopic dermatitis, particularly considering patients presenting eczema within the head and neck region. Various studies prove the presence of antigen-specific IgE and demonstrate positive results of skin prick tests and atopy patch tests with *Malassezia* species in adult atopic dermatitis patients. However, to date, researchers have been unable to confirm such IgE-mediated hypersensitivity in patients with rhinitis and asthma; thus the phenomenon seems to be specific for patients suffering from atopic dermatitis [61, 62, 63].

In the 1980s, David P. Strachan was the first researcher to propose the foundations of the so-called 'hygiene hypothesis', which based on the observation that pollinosis and atopic dermatitis were less commonly present in children from larger families, who were presumably exposed to more infectious agents through their siblings, in comparison to children from families with only one child [64]. According to the 'hygiene hypothesis', children raised in a modern metropolitan life style, relatively devoid of natural microbial exposure, may have under-stimulated immune systems in early infancy, which allows the 'allergic march' to develop – a pattern of pro-allergic immune evolution and disorders that occur in early life [64, 65]. To date, the 'hygiene hypothesis' has been extensively investigated by worldwide specialists, and is considered as an important theoretical framework for the study of various allergic diseases. It attempts to explain an increase in the prevalence of allergy, observed since industrialization, and the higher incidence of allergic diseases in more developed countries [66]. Over the past 15 years, 'hygiene hypothesis' assumptions have evolved, in part due to a growing and strengthening burden of evidence from epidemiological, translational and basic research. Various studies suggest that exposure to some infectious organisms and bacterial endotoxin may provide protect against atopy, whereas other infections appear to promote allergic diseases. What does seem to be important is the timing of exposure to infection, the properties of the infectious agent itself, and also genetic susceptibility of the host – these factors play a significant role in the future development of allergic disease [67, 68, 69].

**Contact allergens and irritants.** Contact dermatitis is defined as a pattern of inflammatory response occurring as a result of contact with certain external factors (contact allergens). Nowadays, over 85,000 chemicals are recognized in the human environment, a predominant part of which may act as irritants, and more than 3,700 compounds have been identified so far as contact allergens. According to data from North America and Western Europe, 12.5%–40.6% of the population are diagnosed as allergic to at least one chemical [70].

The clinical spectrum of contact dermatitis is characterized by a wide range of clinical features: itching, scaling, erythema and vesiculation. In chronic cases, fissuring, hyperkeratosis and lichenification also occur. The two most frequent causes of contact dermatitis are exposure to an irritant substance (irritant contact dermatitis) and a delayed hypersensitivity reaction in response to contact with an allergen in sensitized individuals (allergic contact dermatitis). It is worth emphasizing that the pathogenesis of contact dermatitis often involves contemporary exposure to both irritants and allergens, and these substances often belong to the group of common and prevalent environmental factors. Primary lesions are usually found at the site of contact with the irritant or allergen, but patients suffering from allergic contact dermatitis may also present secondary lesions (so-called secondary allergisation), which may occur on other (even distant) sites of the body. However, the majority of contact dermatitis patients present skin lesions on their hands [71, 72, 73].

Allergic contact dermatitis is a frequent and chronic skin disease, very often associated with environmental factors, mainly of occupational origin. In the 70s and 80s of the 20th century the distribution of contact allergy in Poland differed significantly from the distribution of its western neighbours. The most frequent allergens were chromates, aromatic amines, turpentine and epoxy resins, while the frequency of sensitization to nickel, acrylic plastics and neomycin was lower than in other European countries. Nowadays, only slight differences exist in the occurrence of contact allergy between Poland and Western Europe [73, 74].

One of the most important contact allergens are metals (nickel, chromium and cobalt). In Denmark and Germany, since the European Directive restricting the use of nickel was implemented, a decrease in the frequency of nickel allergy has been noted. In Poland, a so-called 'Nickel Directive' was introduced in 2004, and it has been predicted that the effects of its implementation are likely to be evident only in the course of time. As previously reported, contact allergy to nickel still concerns primarily the young population, and recent observations confirm this phenomenon both in male and female patients.

Recent literature data suggests that important, possible sources of sensitization to metals are metal implants used in various medical disciplines (for example, intravascular stents, dental implants, cardiac pacemakers, or implanted gynecologic devices). Skin hypersensitivity reactions are variable in nature and include eczematous, urticarial, bullous, and vasculitic eruptions [75, 76]. Complex immune reactions which take place around the implants may result in pain, inflammation, and loosening of the implant. Nickel, cobalt, and chromium are considered as the most common metals eliciting both cutaneous and extracutaneous allergic reactions from chronic internal exposure. Occasionally,
other metal ions and bone cement components cause hypersensitivity reactions [77].

Cosmetics, fragrances, and botanicals are also important causes of both irritant and allergic contact dermatitis. The overall incidence of dermatitis produced by cosmetics is rather difficult to determine. Fragrances are important sources of allergic contact dermatitis. Fragrances are found in various types of cosmetics – most traditionally in perfume or cologne form. Fragrances, including fragrance mix, balsam of Peru, and cinnamic aldehyde, are the most commonly identified allergens in cosmetic-induced contact hypersensitivity reactions [78, 79, 80]. Another important source of contact eczema caused by cosmetics are preservatives added to the cosmetic products to prevent their deterioration. There are a number of preservatives used in cosmetics that have been described as eliciting contact dermatitis in sensitive consumers: formaldehyde releasers (agents that slowly liberate small amounts of formaldehyde), methylchloroisothiazoline/methylisothiazolinone (MCI/MI), and parabens. Other important causes of contact allergy include the active ingredients found in hair- and nail-care products, such as permanent wave solutions, permanent hair coloring, artificial nails and nail polishes [79]. An important and potent contact allergen which has lately significantly gained in value is paraphenylenediamine. An increase in contact allergy to paraphenylenediamine has been caused by more frequent hair dying and skin tattooing (also in children), including so called ‘temporary’ henna tattoos. Long-term skin contact and also high concentrations of paraphenylenediamine increase the risk of sensitization. Furthermore, allergic contact dermatitis may be followed not only by post-inflammatory hyper- or hypopigmentation, but also by scarring and lifelong sensitization. This may have an important future occupational impact, especially if a sensitized person chooses to become a hairdresser and/or cosmetician. [79, 80, 81].

With regard to contact dermatitis, it is also important to mention protein contact dermatitis (PCD), which may be provoked by macromolecular proteins (in contrast of hapten, which cause allergic contact dermatitis described above) [72]. PCD is observed mainly in patients with certain characteristics of atopic diathesis, who have frequent contact with the protein products: kitchen workers, food sellers, gardeners, slaughterhouse workers, butchers, commercial anglers, farmers, and veterinarians [82, 83]. Four groups of proteins may be the cause of PCD:
1) fruits, vegetables, spices, and plants (apples, asparagus, bananas, beans, carrots, chrysanthemums, cornstarch, mugwort, peas, peanuts, pears, shiitake mushrooms and soy);
2) animal proteins (blood, bovine amniotic fluid, cheeses, cow dander, egg yolk, meat and milk);
3) flour;
4) proteolytic enzymes (alpha amylase, glucoamylase, lactase)

PCD is considered as closely linked with contact urticaria – urticarial wheals may precede or coincide eczematos lesions, most typically localized on patient’s hands [82, 83, 84].

Emotional factors. Patients suffering from various allergic diseases may present a significantly lower level of self-acceptance, self-knowledge and feeling of self-effectiveness, in comparison to healthy subjects. Skin allergic conditions, including urticaria, allergic contact dermatitis and atopic dermatitis, may be associated with a highly-reduced quality of life, especially considering professional or school activities [85]. Literature data suggests that patients suffering from allergic contact dermatitis and urticaria have a higher prevalence of psychiatric disorders than the general population (mostly anxiety disorders – phobias, followed by depressive and somatoform disorders) [85, 86].

On the other hand, important correlations have been demonstrated between the level of asthma control and the level of anxiety and intensity of depression [85]. The authors suggest that bronchial asthma should be treated as a psychosomatic disease, and various psychological factors are considerably involved in the aetiopathogenesis and clinical presentation of the disease [87, 88]. Attacks of dyspnoea may often be accompanied by a high level of anxiety, mood deterioration, and early identification of patients with bronchial asthma accompanied by such disturbances allows the introduction of appropriate psychosomatic therapy.

It has been observed that stressful situations of a high degree may affect as many as 60-70% of atopic dermatitis patients and cause exacerbation of the disease. Moderate to severe atopic dermatitis negatively affects not only the patients, but also their whole family. The impairment of quality of life caused by childhood eczema has been shown to be greater than or equal to other childhood diseases: asthma, diabetes, emphasising the importance of atopic dermatitis as a major chronic childhood disease [89, 90].

Pruritus, scratching, and sleep problems are common complaints linked to a disturbed quality of life in over 60% of patients. Furthermore, sleep disturbances lead to subsequent tiredness, mood changes, and impaired psychosocial functioning of the child and family, particularly at school and work [90, 91]. Skin scratching and lesions often cause embarrassment, comments, teasing, and social isolation which leads to depression or school and work avoidance. The patient’s lifestyle is limited, considering clothing, holidays, meeting friends, having pets, swimming, or the ability to participate in sporting activities. Atopic dermatitis causes restriction of normal family life and often requires complicated and demanding treatment regimes. The parents of an atopic child may face many difficulties in everyday care, which can cause exhaustion and feelings of hopelessness, guilt, anger or depression. This is why, in case of an atopic patient, the so-called ‘emotional climate’ which includes stability of the family, relationship between parents, relations between siblings, school, and later work atmosphere, is considered as one of the most important elements of the patient’s surrounding. It is important whether life runs relatively smoothly, the parents are connected by bonds of love and friendship, or whether conflicts or irritability influence or affect family cohesion [89, 90, 91, 92].

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