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Emergencies in dermatology

Stany nagłe w dermatologii

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Summary

An emergency is, by definition, a risk for health, consisting in an occurrence of sudden or expected symptoms of health deterioration, the immediate consequence of which may be serious failure in body functions, bodily injury or death. Emergencies in dermatology include a group of skin diseases of various aetiology, with an acute and dynamic course and systemic reactions posing threat to patient's life. A common feature of those diseases is the necessity to undertake immediate medical rescue actions and proper treatment. Though they constitute rare disease entities, each dermatologist should be aware of the emergencies that may occur in dermatology. Quick diagnosis of the disease makes it possible to implement adequate therapy and may considerably decrease the mortality rate, alleviate its course and lower the risk of early and late complications. Further on, the authors or the article describe the most frequent dermatological diseases that require provision of immediate aid to the patient.

Streszczenie

Stan nagły z definicji jest stanem zagrożenia zdrowotnego, polegającym na nagłym lub przewidywanym pojawieniu się objawów pogarszania zdrowia, którego bezpośrednimi następstwami mogą być poważne uszkodzenie funkcji organizmu, uszkodzenie ciała lub utrata życia. Stany nagłe w dermatologii to grupa chorób skóry o różnej etiologii, mających ostry i dynamiczny przebieg oraz objawy ogólnoustrojowe zagrażające życiu chorego. Wspólną cechą tych schorzeń jest konieczność podjęcia natychmiastowych medycznych czynności ratunkowych oraz właściwego leczenia. Choć stanowią one rzadkie jednostki chorobowe, każdy dermatolog powinien zdawać sobie sprawę z nagłych przypadków, które mogą wystąpić w jego pracy. Szybka diagnoza choroby umożliwia wdrożenie odpowiedniej terapii i może znacznie zmniejszyć śmiertelność, złagodzić jej przebieg oraz zmniejszyć ryzyko wczesnych oraz późnych powikłań. Autorzy tego artykułu w jego dalszej części opisują najcięższe dermatologiczne schorzenia wymagające udzielenia natychmiastowej pomocy choremu, tj. zespół Stevensa-Johnsona, toksyczną nekrolizę naskórka, reakcję polekową z eozynofilią i objawami ogólnymi, martwicze zapalenie powięzi, leukocytoklastyczne zapalenie naczyń, a także ostrą pokrzywkę z obrzękiem naczynioruchowym.

Conflict of interest
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STEVENS-JOHNSON SYNDROME (SJS)

Stevens-Johnson syndrome (SJS) was described for the first time in 1922 by Stevens and Johnson, who defined it as 'a new kind of fever with skin eruptions and stomatitis' (1). The disease is recognised as a severe drug-induced reaction, more rarely occurring as the consequence of infectious disease – the herpes simplex viruses type 1 and type 2, varicella zoster virus, cytomegalovirus infection, Epstein-Barr virus, type 6 and 7 herpes viruses, parvoviruses and *Mycoplasma pneumoniae* bacteria (2, 3). SJS prevalence is 1.2-6 cases per one million of people within a year, mainly refer-

ring to persons over 40 years of age. Numerous studies showed the relationship between SJS and over 200 various medicines. Individual groups of medicines were distinguished, the administration of which is subject to an increased risk. These are the following: sulphonamides (co-trimoxazole), anticonvulsants (carbamazepine, lamotrigine, phenytoin, phenobarbital), non-steroid anti-inflammatory medicines from the oxicam group, as well as nevirapine and allopurinol (2). The relationship between the episode and medicine intake is suggested by the fact that a new drug has been administered between 1st and 8th weeks before the occurrence of skin lesions. The average time between drug administration and occurrence of SJS symptoms was estimated as between 6 days and 2 weeks (2). Stevens-Johnson syndrome is a reaction induced by medicines, which activate cytotoxic T lymphocytes that trigger numerous factors responsible for keratinocyte apoptosis. Among the factors most frequently listed by researchers there are: granulysin, the high concentration of which may be found in the liquid inside blisters, perforin, granzyme B and Fas ligand (4). Infectious aetiology may be suspected when infection preceded the occurrence of skin lesions by one week and/or the titre of antibodies in IgM class may be determined, and in case of viral infection, its occurrence is confirmed with the use of a PCR test. At present, the disease is diagnosed when 10% of body surface is covered (3). Clinical symptoms involve sudden onset, high fever, malaise, joint pain and occurrence of skin eruptions in the form of blisters located on the skin, mucous membranes in the oral cavity, nose, sexual organs and conjunctiva. The blisters have poorly tight cover, easily rupturable, hence the clinical image may be dominated by erosions covered with haemorrhagic scabs. Sometimes lining in finger nails can be observed (3, 5). According to various researchers, the mortality rate of SJS oscillates between 2 and 7.5% (2). So far, no consensus has been reached as to the way of treatment of SJS. The core of treatment is early diagnosis and discontinuation of the agent causing the disease, then implementing both symptomatic and causal therapy. The symptomatic therapy involves fluid therapy, painkillers and antipyretic drugs. Glucocorticosteroids and antihistamine drugs are applied in causal therapy, and – in case of infectious aetiology – antibiotics and acyclovir. Local treatment of skin lesions involve application of swabs or creams with antibacterial agents, ointments or steroid creams, as well as biological or biosynthetic dressings (3). Average duration of the disease: 3-6 weeks. Patients with history indicating SJS should avoid using preparations included in the group of high-risk drugs (2, 5, 6).

TOXIC EPIDERMAL NECROLYSIS (TEN)

The notion of 'toxic epidermal necrolysis' was suggested in 1956 by Lyell, when he observed 'toxic skin lesions, resembling burns' in some of his patients. Hence, the disease was also called the Lyell syndrome (7). The majority of authors treat the disease entity as more severe form of the Stevens-Johnson syndrome, with the borderline between them marked by the degree of epidermis lining. Accordingly, TEN is diagnosed when the disease covers > 30% of body surface. In case of lesions covering between 10 and 30% of body surface, the SJS-TEN overlapping syndrome is diagnosed (2). Consequently, toxic epidermal necrolysis is also included to the group of very severe drug-induces disorders, with symptoms of multi-organ insufficiency. The disease prevalence is estimated as 0.4-1.9 cases per million people per annum (2, 8). The mortality rate is 20-50% (4). The etiopathogenesis of toxic epidermal necrolysis is the same as that of the Stevens-Johnson syndrome (2). It is also related to the application of high-risk medicines (sulphonamides, anti-epileptic drugs, non-steroid anti-inflammatory medicines) and to bacterial and viral infections (3). Extensive and rapidly expanding epidermal necrosis is, similarly as SJS, the effect of cytotoxic T lymphocyte activation. Mediators responsible for epidermal necrosis include mainly granulysin, as well as ligand Fas, granzyme B and ligand inducing apoptosis linked to TNF (8). The difference between TEN and SJS is determined by the severity of clinical image of the patient and the possibility of occurrence of more serious complications (2). The initial, so-called prodromal period involves high fever, apathy, eye itching, catarrh and pharyngitis, occurring usually 1-10 days before the occurrence of basic symptoms. Then, there occurs the full-blown period, characterised by erythema on the face and trunk. Next, there occur blisters filled with serous liquid, which are subsequently exfoliated, leaving behind bleeding erosions, covered with scabs in the ultimate period. There occurs the Nikolsky sign, consisting in epidermal lining of the apparently healthy skin during its rubbing. The lesions also involve mucous membranes, initially as oedema, and then self-rupturing formed blisters, transforming into bloody erosions covered with grey quasi-membranes (3, 5, 8). The process covers the respiratory system in 30%. Lesions are also visible on mucous membranes of the digestive tract and urogenital system. If no immediate assistance is provided, the next stage involves occurrence of such complications as loss of liquids, with subsequent dyselectrolitemia and renal insufficiency, secondary bacterial infections complicated by sepsis, adhesions of mucous membranes (stenosis of anus, urethra, vagina), ulcerations of cornea, conjunctiva, adhesions of eyelids and even blindness (3, 6). In case of proper treatment, the period of treatment and recovery lasts several weeks. Distant complications are diagnosed in 29% of cases and these mainly involve: skin discolorations, scars, dry conjunctivitis, photophobia, deformations of nails and others (3). Patients with TEN should be treated at the intensive medical care unit or burn treatment ward. The core therapy involves discontinuation of the suspicious medicine, which considerably improves the prognosis. Disease severity is evaluated with the use of SCORTEN

scale. It consists of 7 clinical and laboratory ratios. Each rate equals 1 score. According to the said scale, the mortality rate increases from 3.2% for 0-1 score to > 90% for > 5 scores (2). In order to accelerate elimination of the suspicious drug from the circulatory system, high doses of N-acetylcysteine are sometimes administered (2). The most frequently applied therapies involve mainly glucocorticoids, immunoglobulines and cyclosporin A (8). Though glucocorticoids show immunosuppressive effect, they inhibit the activity of cytotoxic T lymphocytes and they have been mainly used in high doses during initial periods of the disease, the current British guidelines do not recommend their application due to the involved higher risk of infections, longer hospitalisation time and increased mortality rates (9). Intravenously administered immunoglobulins became the most recognised therapy in TEN. The immunoglobulins suppress keratinocyte apoptosis through Fas receptors inhibition (9). European guidelines suggest they may be used during the initial stage of the disease, though they are reported to be ineffective (10). Cyclosporin A is another immunosuppressive drug used in TEN therapy. Its administration is attributed to faster healing of the epidermis. Basing on French studies, the accepted dose of cyclosporin A amounts to 3 mg/kg of body weight for 7 days. After that period, the dose should be reduced (9, 11). It is suggested that TNF alpha inhibitors may serve as an important treatment agent. Infliximab used in a single dose of 5 mg/kg proved effective, quickly improving skin lesions. Etanercept, another TNF alpha inhibitor, in a single dose, also makes the epidermis regeneration faster, while not causing deaths, despite the initially estimated mortality rate of 50%. On the other hand, thalidomide turned out to be detrimental, since it paradoxically increased the mortality rate (2, 8, 9). Summing up, the pharmacological procedure is still controversial, because there are not enough randomised studies. The basis for therapy is normovolaemia, efficient analgesia and counteracting infections.

DRUG RUSH WITH EOSYNOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

Another disease that poses a potential risk to human life is a drug rush with eosinophilia and systemic symptoms (the so-called DRESS syndrome). The prevalence is 1.2-6:1 000 000 per annum, and is higher in patients taking anticonvulsants (12). DRESS is an example of rare hypersensitivity to drug. Since skin contains the most numerous population of immunocompetent cells, it is the most susceptible to the development of hypersensitivity reactions. Additionally, skin may metabolise drugs extrahepatically (12). The pathogenesis of DRESS involves many factors and has not been fully explained yet. The disease is characterised by fever, lymphadenopathy, skin and hematologic reactions and dysfunctions of internal organs (13). The mortality rate is 10-38% (14). The course of disease depends on the condition of internal organs (13). No symptom is pathognomonic for the said disease. The word 'eosinophilia' in its name is not a sufficient indicator to state the diagnosis. The disease usually develops in 3-8 weeks, following drug administration to predisposed patients, who suffer from dysfunction of the detoxication mechanisms of drug metabolism, activation of keratinocytes, macrophages and T lymphocytes (13). The mechanism is known as idiosyncrasy – individual variable reaction to a medicine (12). Metabolites related to histocompatibility antigens on keratinocytes activate lymphocytes to generate interleukins, which further intensify the cytotoxic activity of lymphocytes. Among the medicines that may lead to DRESS, we can list aromatic anticonvulsants, such as carbamazepine, phenytoin, phenobarbital, lamotrigine, as well as allopurinol, sulphonamides and dapsone. The contributing factor may be viral infections, mainly HHV-6 and HHV-7, as well as EBV (12, 13). In the study covering 100 patients with DRESS syndrome, HHV-6 was detected in almost 60% of them (15). Skin eruptions are polymorphic. Erythema and papular rush are the most common, but there may also appear urticaria blisters, pimples, blisters, erythemic and exfoliating lesions. Hematologic deviations may include either eosinophilia, neutrophilia, neutropenia, thrombocytopenia and hemolitic anaemia (12). Though dysfunctions of internal organs most commonly involve liver, kidneys and lungs, the lesions may occur in each organ (14). According to RegiSCAR group, which determined diagnostic criteria for DRESS, the syndrome may be recognised in patients taking drug with a skin rash, which additionally show 3 from 4 the following criteria: fever, lymphadenopathy, haematologic disorders and infected internal organs (12). The most important aspect in DRESS therapy is discontinuation of the suspicious drug and implementation of general glucocorticosteroids therapy (14). A therapy involving intravenous administration of immunoglobulins is also possible and – in severe cases – a plasmapheresis. N-acetylcysteine may also be administered to eliminate the medicine faster from the circulatory system (12). In the majority of cases, the symptoms regress within 3 weeks, whereas the course may be various: from weak to severe. The most serious stage of the disease usually occurs several days after drug discontinuation. There are reports of autoimmunologic diseases developing in patients who formerly suffered from DRESS (13).

NECROTIZING FASCIITIS (NF)

It is another disease with potential risk to human life. Its prevalence worldwide is estimated as 0.4 for 100 000 per annum and shows an increasing trend (16). It is a rapidly developing bacterial infection of soft tissues. The infection is spread mainly along the fascia. It requires quick diagnosis and immediate implementation of treatment, including surgery. Initially, there occurs erythema and oedema, then smaller and bigger blisters, and, subsequently, necrosis of tissues. The accompanying symptoms involve intensified pain, also occurring in the apparently healthy skin, fever,

tachycardia and drop in arterial blood pressure leading to multi-organ insufficiency (17). Necrotic pathogenesis of fasciitis necrotizing involves activity of litical enzymes (hyaluronidase, streptokinase, streptolysin), generated by bacteria which damage the vascular endothelium, forming clots and haemorrhage, leading to further tissue necrosis (18). Depending on the aetiology, 4 types of necrotizing fasciitis were distinguished. Type I – the most common one (55-90%), induced by mixed bacterial flora. People with immunodeficiency are the most exposed to the disease, for instance, those with concurrent diabetes. Type II – infection is induced by *Streptococcus pyogenes*, independently, or in conjunction with *Staphylococcus aureus*. It strikes healthy persons, and the infection is spread through micro-damages in the skin and petty injuries. It may appear iatrogenically during injections. Its possible complications may be a toxic shock and multi-organ insufficiency. Type III of necrotizing fasciitis is induced by *Clostridium* spp., as well as by *Vibrio vulnificus*. This type has a striking course and high mortality rate, estimated as 35-44%, even when implementing a correct therapy. Type IV is caused by fungal infection, most commonly by *Candida* spp., as well as *Zygomycetes* (17, 19, 20). The diagnosis involves clinical symptoms, image tests (USG, CT, X-RAY), microbiologic and histopathologic tests (17). Undoubtedly, diseases with related immunodeficiency are among the risk factors of necrotizing fasciitis. The disease is commonly described in patients with diabetes, arterial hypertension, obesity, chronic renal failure. Other risk factors also involve the following: alcohol abuse, HIV infection, drug addiction and surgical operations (16, 18, 19). Two factors must be taking into account when trying to efficiently treat NF, namely the awareness of the disease despite its rare occurrence and, concurrent immediate antibiotic and surgical therapy. The key of successful therapy of necrotizing fasciitis is quick implementation of surgical treatment (17, 18, 21). Fast cleaning of necrotic tissues decreases the mortality rate and considerably improves the prognosis. It is not recommended to delay surgical operations by using diagnostic methods. The main objective of surgical interventions should involve resection of all infected parts of the fascia, providing for some healthy adjacent parts. Additionally, necrotic skin and soft tissues caused by thrombosis should be removed. Surgical interventions should be repeated until all necrotic tissues are dissected. Smears from the wounds may be taken during each operation (17, 21). Occlusive dressings or vacuum therapy may be applied only when anaerobic infections are excluded (17). Antibiotics constitute an obligatory therapy supporting surgical operations. At present, the recommended empirical therapy involves the application of ampicillin with or without sulbactam with clindamycin or metronidazole. Alternatively, cephalosporins with clindamycin or metronidazole may be administered. Following an antibiogram, a targeted therapy should be implemented (22).

VASCULITIS LEUKOCYTOCLASTICA

This expression includes a heterogeneous group of diseases relating to hypersensitivity to antigens. The lesions involve capillary vessels, small veins and arterioles (23). Among the most common responsible agents we may list medicines, foreign proteins, certain chemicals and systemic diseases of connective tissue, insect bites and tumours (24, 25). More than one half of the cases have idiopathic background. The prevalence is about 30 cases per million people per annum (23). The prevalence is distributed evenly among men and women (23). Typically, the symptoms involve painful, burning palpable spotty rash, appearing symmetrically, mainly on the lower limbs. One third of the patients have skin lesions also on their upper limbs and trunks (26). Spotty lesions occur when erythrocytes permeate through the damaged wall of blood vessels; they do not turn pale under pressure and do not result from thrombocytopenia (25). Additionally, there may appear urticaria blisters, papules, small haemorrhagic blisters, subcutaneous tissue oedema and livedo reticularis (24). The accompanying symptoms involve malaise, joint and muscle pain and fever (26). Though the exact pathomechanism is not known yet, the symptoms are triggered by circulating immunological complexes, which subsequently accumulate in the capillary walls, activating the complement system (type III of the hypersensitivity) (24). Then, the active elements of the complement, mainly C5a and C3a attract granulocytes and macrophages, which release cytokines and lysosomal enzymes (collagenase, elastase, myeloperoxidase) damaging vessel walls (27). The diagnosis may be confirmed with the use of a histopathological test, which reveals perivascular leucocyte infiltrations with prevalent neutrophiles, their cell nuclei (leukocytoclasis) and fibrinoid necrosis of blood vessel walls, as well as endothelial cells oedema (26). Occurring pain in joints or symptoms of arthritis require administration of non-steroid anti-inflammatory drugs and – sometimes – orally administered steroids (prednisone, methylprednisolone) in the dose of 1 mg/kg of body mass for 4 weeks in reduced doses (23). The majority of cases have moderate course of disease, more severe cases involve patients with systemic vasculitis (synovial fluid, lungs, pericardium, digestive system and kidneys). Kidney infection (microhematuria, proteinuria) determines severe course of the disease and makes the prognosis considerably worse. The symptoms usually disappear in 3-4 weeks. 10% of the patients do not show any remission and the symptoms become chronic or recurrent (26). The therapy involves generally administered corticosteroids anti-histamine and non-steroid anti-inflammatory drugs (25). Some patients require the application of immunosuppressive medicines, such as azathioprine or cyclophosphamide. In chronic cases, the colchicine is used. Particularly severe and unfavourable course of the disease may occur when the digestive tract is infected (acute abdomen symptoms) (25). Morgado et al. described a case of

a 71-year old woman with the leukocytoclastic vasculitis, who took ciprofloxacin because of the digestive tract infection. Typical skin lesions appeared four days after the implementation of antibiotic therapy. After a few consecutive days, there occurred gastrointestinal bleeding. Gastroscopy showed vasculitis of mucous membranes in the stomach and duodenum, similar to the observed skin lesions. The histopathological test of the skin biopsy showed neutrophil infiltrations and fibrinoid necrosis of blood vessel walls. Skin and mucous symptoms disappeared after antibiotic discontinuation and steroid therapy implementation (26).

ACUTE URTICARIA WITH HEREDITARY ANGIOEDEMA

The urticaria is characterised by sudden occurrence of urticaria blisters or angioedema or both symptoms concurrently (27). Actually, urticaria blisters constitute dermal oedema, with accompanying itching. It is of temporary nature, it usually disappears with no traces within 24 hours. Angioedema involves deeper layers of the subcutaneous tissue. The lesions are less protruding than in case of urticaria and occur mainly in the areas of loose connective tissue (face, eyelids). It may also involve submucosal parts of the oral cavity, throat, larynx or even the gastrointestinal mucous membrane. Pain is more common than itching in this case. It usually disappears with 72 hours (27, 28). Acute urticaria is diagnosed when the symptom last up to 6 weeks (29). The risk of acute urticaria occurrence in the total population is 20% (27). Hereditary angioedema and/or urticaria prevalence in the US is 25% (29). Hereditary angioedema is mediated mainly through histamine and, though notably less frequently, with the use of bradykinin. The hereditary angioedema accompanying urticaria may be either allergic or non-allergic, while congenital or acquired angioedema usually does not accompany urticaria. The diagnosis determining which factor mediates in the angioedema is of particular importance, in order to implement a relevant and efficient therapy. Angioedema mediated by histamine responds to treatment with the use of antihistamine drugs, glucocorticosteroids and epinephrine. Angioedema mediated by bradykinin does not respond to such therapy. Increased use of angiotensin convertase inhibitors during the last several decades caused higher prevalence of angioedema induced by these drugs (28). Acute urticaria and/or hereditary angioedema symptoms may occur in patients formerly allergic to food products, drugs, pollens and other allergens. Infections, consumption of food, drugs, occupational exposure, insect venoms preceding the occurrence of the symptoms make it possible to narrow the search to several agents only (27, 29). Acute urticaria may accompany acute infections in children. Cases were described involving urticaria reactions linked to Epstein and Barr virus infections, viral hepatitis (types A, B and C) and gastrointestinal parasites (29). Among the foodstuffs most commonly inducing acute allergic urticaria we may list nuts, peanuts, fish, crustacea, wheat, eggs, soya and fruit. Urticaria may also be induced by food additives, such as benzoates, sulphites, monosodium glutamate, food colouring agents and other agents (29). In case of diagnosed urticaria with hereditary angioedema one must, first of all, make sure whether there are no respiratory disorders (hoarseness, laryngeal stirdor, difficulties in swallowing). Laryngeal oedema is particularly dangerous and poses risk to human life. Intubation, cricothyrotomy or tracheotomy may be required (28). The therapy involves the use of antihistamine drugs inhibiting H1 and H2 receptors, as well as glucocorticosteroids. Administration of antihistamine drugs for several weeks may suppress urticaria reactions and lead to full remission of symptoms (27). In case of respiratory tract infections that pose threat to life or a hypotension, it is recommended to administer 0.2-0.5 mg of adrenaline, intramuscularly (28). In case of acquired or hereditary angioedema, a freshly frozen plasma, C1 inhibitor complement concentrates and callikrein inhibitors may be used (28).

CONCLUSIONS

Though they constitute rare disease entities, each dermatologist should be aware of the emergencies that may occur in dermatology. Quick diagnosis of the disease makes it possible to implement adequate therapy and may considerably decrease the mortality rate, alleviate its course and lower the risk of early and late complications.

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