Toxic epidermal necrolysis

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Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), also known as Lyell’s syndrome, are rare, life-threatening diseases that are characterised by extensive epidermal detachment, erosion of mucous membranes and severe systemic symptoms. In the majority of cases, the development of symptoms can be attributed to the use of drugs; therefore, the disease pathology is thought to be caused by a severe adverse reaction to drugs. The high mortality rate results primarily from the development of complications in the form of systemic infections and multiple organ failure. TEN and SJS affect all age groups, including newborns, infants and older children. The rarity of these syndromes has not permitted large, randomised studies, which has resulted in numerous difficulties in their diagnosis and management. Because the pathogenesis has not yet been established, the management and systemic treatment of these syndromes have not been standardised. The efficacy of the treatment options suggested has not been confirmed by clinical studies involving suitably large groups of patients, especially children.

Key words: intensive care, children; toxic epidermal necrolysis, pathogenesis, toxic epidermal necrolysis, treatment, Stevens-Johnson syndrome

Stevens-Johnson syndrome (SJS) was first described in 1922 by Stevens and Johnson [1] in two children as acute fever with skin eruptions and stomatitis. The term “toxic epidermal necrolysis” (TEN) was suggested in 1956 by Lyell when he observed toxic skin lesions resembling scalding in 4 patients [2]; hence, this disease is also known as Lyell’s syndrome. Bastuji-Garin [3] noted the overlap between SJS and TEN in terms of their clinical, aetiological and histopathologic features. She recognised that both syndromes are variants of the same disease that vary in the extent of the skin lesions and thus suggested new definitions. Accordingly, SJS is diagnosed when the epidermal detachment involves less than 10% of the body surface area; SJS/TEN overlap is diagnosed when 10−30% is affected; and TEN is diagnosed when more than 30% of the body surface is affected (3.40).

The incidence of SJS is 1.2–6 cases, and that of TEN 0.4−1.9 per million individuals per year [5−7]. The estimated incidence of all three forms, i.e., SJS, SJS/TEN overlap and TEN, is 2−7 per million per year. Three-fold higher incidence rates are observed in HIV carriers, i.e., $1 \times 10^{-3}$ [8]. Moreover, the incidence of SJS/TEN increases with age and the coexistence of other ailments. This syndrome is associated with reduced immunity and the administration of numerous drugs, which can lead to drug interactions and, ultimately, to the development of adverse post-drug reactions.

The mortality rate of SJS/TEN was initially extremely high, particularly for TEN, ranging from 25 to 70% [9]. Advances in maintenance treatment and the early admission of patients to burn care departments or ICUs contributed to a reduction of the mortality rate to 1−5% for SJS and 25−30% for TEN [10, 11]. The mortality rates in the paediatric population are substantially lower. In their comparative analysis, Levi and co-workers [12] studied 80 affected patients and 216 controls, all of whom were under 15 years of age. The mortality in this group was 7.5%. Similar mortality rates in the paediatric population were observed in studies based on case series. According to Spies and colleagues [13] and Ferrandiz–Pulido and colleagues [14], the mortality was 7%; Finkelstein and co-workers [15] found it to be even lower, i.e., 2%.

AETIOLOGY

In the majority of cases, SJS/TEN are caused by medications or, to a lesser degree, by infectious factors. Based on
their 10-year experience with the treatment of SJS/TEN in children, Forman and colleagues [16] demonstrated that SJS was induced by drugs in 91% of cases and by infectious agents in 4.5% but that TEN was caused exclusively by drugs.

The findings of numerous studies have revealed a correlation between SJS/TEN and over 200 different drugs, with the high-risk group including sulphonamides (cotrimoxazole, sulfasalazine), anticonvulsants (lamotrigine, carbamazepine, phenobarbital, phenytoin) as well as allopurinol, nevirapine and non-steroidal anti-inflammatory drugs (NSAIDs) of the oxicam group, aminopenicillins, cephalosporins and quinolones [17]. The studies primarily involved adults. Considering the differences between adults and children regarding the types of drugs administered, some authors have confirmed the list of drugs in children. According to Levi and colleagues [12], the high-risk group included sulphonamides and anticonvulsants. A substantial risk was also found to be associated with valproic acid, NSAIDs and paracetamol. No cases caused by allopurinol, nevirapine or oxicam were observed. Forman and colleagues [16] demonstrated a correlation between SJS/TEN sulphonamides and both penicillins and cephalosporins. Similar results regarding children were reported by Spanish authors [14]. In their study, the most common causes of SJS/TEN were anticonvulsants (carbamazepine, lamotrigine, phenytoin), followed by antibiotics (penicillins, macrolides) and NSAIDs, except for oxicam. Of note, the substantial-risk group contained paracetamol. Several reports have described cases of SJS/TEN following the use of paracetamol [18]. The study involving 32 paediatric patients additionally showed that ibuprofen significantly worsened the course of disease and increased the risk of complications [19].

The infectious agents associated with SJS/TEN in the paediatric population predominantly include Mycoplasma pneumoniae, viruses (influenza, Epstein-Barr, herpes 6 and 7, cytomegaloviruses, parvoviruses, coxsackie viruses), bacteria (β-haemolytic streptococci), mycobacteria and rickettsia [20]. However, it has not been demonstrated whether infectious agents directly cause SJS/TEN or are cofactors when combined with drugs. The infectious aetiology of SJS/TEN can be suspected when the infection preceded the skin lesions by 1 week and/or the titre of IgM antibodies can be determined. In contrast, a correlation between the development of disease and drug use suggests that a new drug was added 1-8 weeks prior to the appearance of the skin lesions. Generally, the average time between the administration of drugs and the occurrence of symptoms ranges from 6 days to 2 weeks [21].

**IMMUNOPATHOGENESIS**

The pathogenesis of SJS/TEN has not been elucidated and is the subject of numerous studies. The detachment of the epidermis in TEN is caused by the necrosis of keratinocytes following apoptosis [22]. The cells responsible for apoptosis are CD8+ T lymphocytes [23]. The exposure to a drug induces their maturation into cytotoxic T lymphocytes. Two theories exist regarding their mechanism of activation. The first theory is based on the pharmacological interaction of the drug and the immune system. According to this theory, the drug stimulates the immune system via non-covalent binding directly with the major histocompatibility complex I (MHC) and T cell receptors. The second theory, based on the pro-hapten/hapten reaction, states that drug metabolites bind covalently to cell proteins, which leads to the formation of molecules capable of stimulating the immune system [21, 24].

Many factors have been implicated to be responsible for keratinocytes apoptosis, and granulysin is currently considered the main cause. Chung and colleagues [25] found two- to four-fold higher concentrations of granulysin in the blister fluid compared with the concentrations of perforin, granzyme B and soluble Fas ligand. Additionally, a correlation between the concentration of granulysin in the blister fluid and the severity of disease has been demonstrated [24]. Fas ligand, another factor involved in apoptosis, is a transmembrane protein that is found in the cell membranes of cytotoxic T lymphocytes, NK cells and keratinocytes and can be detached from the cell membrane surface into its soluble form (sFasL) [26, 27].

Moreover, granzyme B and perforin are considered to be apoptotic factors in TEN. They are secreted together with granulysin by activated T lymphocytes. The role of TNF-α in the pathogenesis of TEN is also being investigated. Its concentration in the blister fluid, skin and serum of TEN patients has been found to be increased [21]. Viard-Leveugle and colleagues [28] emphasised the involvement of nitric oxide (NO) in apoptosis. TNF-α and INF-γ secreted by activated T cells increase the expression and activity of induced NO synthetase (iNOS) in keratinocytes. Increasing levels of NO result in the increased expression of FasL in keratinocytes and lead to Fas- and caspase 8-mediated cell death.

**DIAGNOSIS**

In many cases, it is extremely difficult to identify which particular drug is responsible for SJS/TEN because individual patients may take many medications. Therefore, diagnostic tests are being developed that would facilitate the identification of a harmful agent.

In 2010, an algorithm of drug causality for epidermal necrolysis (ALDEN) was suggested [29]. The results of ALDEN were found to be consistent with those of the EuroSCAR study. Because the course of disease of SJS/TEN is severe, tests with the subcutaneous administration of the drug that is suspected
of inducing symptoms and with re-exposure to the drug are not recommended [11]. Epidermal patch tests are suggested [30], but their sensitivity for SJS/TEN is low. At present, ex vivo/in vitro testing is being evaluated. The lymphocyte transformation test (LTT), which measures the in vivo transformation of T lymphocytes induced by the drug, shows a sensitivity of 60−70% in patients who are allergic to β-lactam antibiotics; however, in the case of SJS/TEN, its sensitivity is markedly lower [11, 31]. Another in vitro test is based on an increase in the expression of CD69 antigen on T lymphocytes two days after stimulation with the drug, which indicates hypersensitivity to the drug. Furthermore, the use of immunochromatographic analysis has been suggested, which enables the detection of high concentrations of granulysin in serum. When used 2−4 days before the occurrence of mucous membrane erosion, it shows a sensitivity of 80% and a specificity of 95.8% [32]. All of the tests mentioned above require further studies to determine their usefulness for the diagnosis of SJS/TEN.

When an infectious aetiology is suspected, serological tests are needed to determine the IgM and IgG titres. In addition, the polymerase chain reaction (PCR) method is recommended for the diagnosis of herpes simplex virus, varicella, Epstein-Barr virus, herpes 6 and 7 viruses, parvoviruses and Mycoplasma pneumoniae [20].

CLINICAL SYMPTOMS

Generally, the development of SJS/TEN is preceded by non-characteristic prodromal symptoms, such as pharyngitis, fever, apathy, headaches, eye itch or dysphagia, which occur approximately 1−10 days before the appearance of the main disease symptoms [20, 21].

The variability and dynamics of the presentation in children and in adults are similar. The skin lesions are initially located on the face and trunk, assuming the form of red spots and papules merging into generalised erythema multiforme. Subsequently, blisters filled with serous fluid develop that exfoliate leaving ulcerations with areas of necrosis and bleeding, painful erosions and finally crusts. The above process gradually affects an increasingly large area of skin and mucous membrane (though rarely in small children). The presence of the Nikolsky’s sign, i.e., apparently normal epidermis exfoliating when slightly rubbed, can suggest toxic epidermal necrolysis [20].

Acute injuries to the skin and mucous membranes are accompanied by symptoms in other organs: conjunctival ulceration with purulent inflammation, painful inflammatory ulcerated lesions in the airway, gastrointestinal tract and sexual organs that manifest as bleeding and evidence of infection [14].

As TEN progresses, patients are likely to develop respiratory failure in the course of pneumonia or pulmonary oedema, acute renal injury most likely from cytokine-induced injuries to proximal tubules and the glomerular filtration system. In addition, sepsis, liver failure or myocarditis can develop [14, 21].

DIFFERENTIAL DIAGNOSIS

With regard to the dermatologic symptoms, SJS/TEN should be differentiated from erythema multiforme, staphylococcal scalded skin syndrome (SSSS), linear IgA bullous dermatosis, graft-versus-host disease (GVHD), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS), generalised measles-like drug rash and pemphigus vulgaris or paraneoplastic pemphigus [32].

PREVENTION

Patients with a history suggestive of SJS/TEN should avoid high-risk medications. Attention should be paid to possible cross-reactivity of certain drug groups, e.g., anticonvulsants [32].

Numerous studies indicate genetic predispositions to drug hypersensitivity reactions, which are strongly associated with the major histocompatibility complex. Studies of the Han population have demonstrated a 100% correlation between human leukocyte antigen (HLA)-B*1502 and hypersensitivity to carbamazepine as well as HLA-B*5801 and allopurinol. A correlation between HLA-B*1502 and carbamazepine has not been confirmed in the European population; however, the correlation between HLA-B*5801 and allopurinol was found to be weaker in the European population than found in Asian studies, i.e., 61%. The other correlations observed in the European population concerned HLA-B*5701 vs. abacavir and HLA-B*3101 vs. carbamazepine [21, 24, 33, 34].

Genetic tests performed before the use of drugs can prevent SJS/TEN in some groups of patients. The Food and Drug Administration (FDA) recommends the HLA-B*1502 test in patients of East Asian origin before the administration of carbamazepine and the HLA-B*5701 test in all patients prescribed abacavir [32].

TREATMENT

No consensus standard treatment, particularly in children, has been established for SJS/TEN, which reflects the small number of patients studied [9, 20, 35]. An essential issue underscored in the literature is the need for early, rapid diagnosis, withdrawal of the causative agent inducing the inflammatory reaction, implementation of treatment and transfer of patients to specialised centres, which have been shown to decrease the incidence of complications and mortality rates [20]. To achieve a good therapeutic outcome, the cooperation of the team of specialists is essential. Local treatment of skin lesions involves surgical debridement under
general anaesthesia, the application of biological and biosynthetic dressings acting as a protective barrier and steroid and antibiotic ointments [32]. The recommended management includes intensive care with provision for central vascular accesses, invasive monitoring of vital functions, full aseptic conditions, prevention of eye injuries, monitoring of infections, pain management, sedation, respiratory support, maintenance of fluid balance, parenteral nutrition covering increased energy requirements, and maintenance of optimal room temperature, i.e., 30–32°C. Fluid requirements fulfilled by the supply of compound electrolyte solution (CES) was determined at 2 mL kg⁻¹ % of affected body surface-1 or CES, 0.7 mL kg⁻¹ % of affected body surface-1 plus 5% albumin solution in the amount of 1 mL kg⁻¹ % of affected body surface-1 (according to Mockenhaupt). Antibiotic prophylaxis is not recommended; if an infection develops, targeted therapy is advised [20, 24, 32].

There is no gold standard for the treatment of the underlying pathology; two therapies of SJS/TEN in children are widely accepted, although both arouse controversy.

The therapies used most commonly are intravenous immunoglobulins (IVIGs) and corticosteroid pulses [11, 24, 36]. By blocking Fas receptors, IVIGs inhibit the apoptosis of keratinocytes. IVIGs in a dose of 2–4 g kg⁻¹ administered during the first 4 days have been reported to inhibit the evolution of skin lesions, shorten the disease duration and improve the survival rates [20]. However, other studies did not confirm the above findings [11, 37]. The role of corticosteroid therapy is also being disputed. According to some studies, the therapy results in good outcomes only when corticosteroids are administered in large doses during the first days of the disease; moreover, the risk of complications in cases of prolonged use of these drugs has been emphasised [9, 20]. Completely different opinions have also been reported. For instance, according to Chave [38], corticosteroids can be harmful (increased risk of sepsis and increased mortality), are ineffective and should not be recommended for the treatment of TEN.

The second-line drugs and therapies include cyclosporine, infliximab and plasmapheresis used in various combinations. Cyclosporine, an immunosuppressant, has been used to treat SJS/TEN for several years and is associated with good outcomes, i.e., the rapid re-epithelialisation of the skin. It inhibits the immune responses mediated by T lymphocytes, macrophages and keratinocytes and affects the production of inflammatory mediators. Modifications of the doses and duration of treatment can reduce the risk of side effects, which are lower than those incurred by cyclophosphamide or thalidomide. However, the development of complications should be taken seriously, e.g., kidney dysfunction, neutropaenia or leukodystrophy; monitoring the serum drug concentrations is thus required [11, 32, 39].

Another immunosuppressive and immunomodulatory preparation is infliximab, which most likely blocks the apoptotic effects of TNF-α [40]. Infliximab is also used to treat other immunological diseases and is being tested in larger populations of patients [41, 42].

Finally, plasmapheresis has also been applied to treat SJS/TEN and has resulted in good outcomes in both adults and children [11, 20, 43, 44]. Generally, it is used after pharmacological therapy (IVIGs and corticosteroids) when lesions progress or when there is no improvement in the patient’s condition.

The treatment and recovery usually last several weeks or longer and late complications can develop [45]. According to Ferrandiz-Pulido [14, 20], late complications occur in approximately 29% of cases and include skin discolouration, nail deformities, chronic ulcerations of the oral cavity and sexual organs, lingual papilla atrophy, photophobia, dry conjunctivitis, conjunctival adhesions, impaired growth of lashes, and blindness. Finkelstein [15] assessed the incidence of late complications at 47%. In the majority of cases, skin discolouration and scars (42%) as well as various types of vision impairment (27%) are observed; the remaining ones include phimosis, bronchitis, cholangitis and venous thrombosis.

PROGNOSIS

In 2000, Bastuji-Garin and co-workers [46] suggested using the SCORé of Toxic Epidermal Necrosis (SCORTEN) scale to evaluate the risk of death among patients with SJS/TEN admitted to specialised departments. Seven independent death risk factors were established; based on these risk factors, a severity-of-illness scale and predicted mortality rates were determined (Table 1).

### Table 1. The SCORTEN scale (according to [46])

<table>
<thead>
<tr>
<th>Risk factor: score of 1 each</th>
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<tbody>
<tr>
<td>Age &gt; 40 years</td>
</tr>
<tr>
<td>Heart rate &gt; 120 min⁻¹</td>
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<tr>
<td>Concomitant malignant neoplasm</td>
</tr>
<tr>
<td>Epidermal detachment &gt; 10% of body surface</td>
</tr>
<tr>
<td>Serum urea level &gt; 10 mmol L⁻¹</td>
</tr>
<tr>
<td>Serum levels of bicarbonate &lt; 20 mmol L⁻¹</td>
</tr>
<tr>
<td>Serum levels of glucose &gt; 14 mmol L⁻¹</td>
</tr>
<tr>
<td>Mortality rates — scores</td>
</tr>
<tr>
<td>0–1 — 3.2%</td>
</tr>
<tr>
<td>2 — 12.2%</td>
</tr>
<tr>
<td>3 — 35.5%</td>
</tr>
<tr>
<td>4 — 58.3%</td>
</tr>
<tr>
<td>&gt; 5 — 90.0%</td>
</tr>
</tbody>
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To achieve a higher accuracy, the assessment should be performed on post-ICU admission day 1 and 3 [47].

The SCORTEN scale was formulated based on adult populations; hence, its usefulness for pediatric patients requires further study. According to Hamilton and colleagues [35], better prognostic factors of mortality in the pediatric population are the pediatric index of mortality (PIM 2) and pediatric logistic organ dysfunction (PELOD) commonly used in pediatric ICUs.

With regard to prognosis, various indices of homeostasis disorders are also being studied. Yeong and co-workers [48] have demonstrated forty-fold higher mortality rates in TEN patients with concentrations of bicarbonates lower than 20 mmol L\(^{-1}\). Yun and colleagues [49] have suggested the determinations of lactate dehydrogenase in the early stages of SJS/TEN to evaluate the severity of disease. Furthermore, Ducic and co-workers have devised a formula to calculate the mortality rates based on three risk factors affecting the prognosis, i.e., symptoms of sepsis on admission, advanced age and the body surface area affected [32].

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