Case report

STEVENS-JOHNSON SYNDROME –TOXIC EPIDERMAL NECROLYSIS:induced by LAMOTRIGINE in a 15-year-old girl- case report.

Abstract :

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are immune complex-mediated hypersensitivity reactions and have been associated with numerous adverse drug side effects.
Lamotrigine (LTG), an anticonvulsant and mood stabilizer drug, may be associated with this adverse reaction affecting the skin and mucous membranes.
SJS carries high mortality and morbidity and requires special attention as the use of LTG is increasing in clinical practice. We present a case where the patient developed Stevens-Johnson syndrome at 2 weeks after starting LTG treatment.
The case is discussed because of its relevance to the use of LTG which is commonly prescribed by neurologists and psychiatrists and whose use should be stopped at the appearance of skin-mucous membrane rash.

Keywords:Stevens-Johnson syndrome, toxic epidermal necrolysis, lamotrigine.

Introduction:

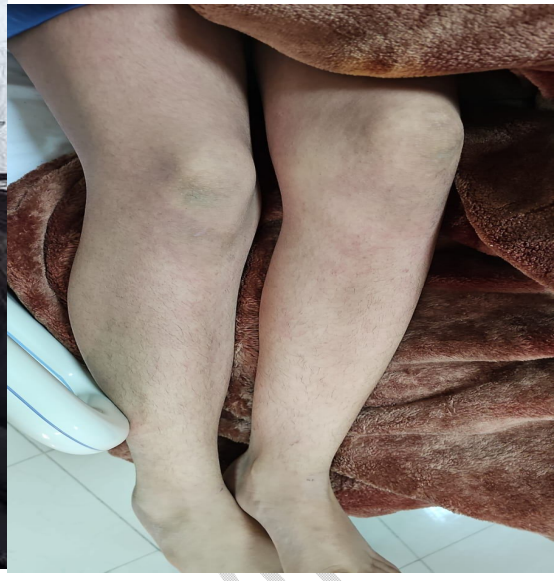
Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or Lyell syndrome are acute, life-threatening cutaneous hypersensitivity reactions. They are most often linked to medication.
SJS and TEN are characterized by keratinocyte apoptosis of the cutaneous and mucosal epithelia. The lesions will gradually coalesce and cause more or less extensive epidermal detachment. (1)
Lyell syndrome and SJS therefore belong, due to their clinical, histological, etiological and pathophysiological similarities, to the same spectrum of disease: epidermal necrolysis (EN).
A classification based on the percentage of maximum detached–detachable body surface area (BSA) has been proposed. (2)
Stevens-Johnson syndrome is considered a milder form of NET and the affected body surface area is less than 10% (3).
Although considered a rare event, SJS is more common in adults than in children.
Most cases of anticonvulsant-induced SJS and TEN have been reported after puberty and in young adults, with rare cases of onset in infancy or early childhood. (4)
Clinical features of SJS include significant involvement of the skin and mucous membranes of the mouth, nose, eyes, vagina, urethra, gastrointestinal tract, and lower respiratory tract. (5)
Drug-induced lesions occur within 4 to 28 days (maximum 56 days) of drug intake (usually the first in life) and continue to appear as eruptions for 2 to 3 weeks. (6)
The rash may begin as macules that develop into papules, vesicles, bullae, urticarial plaques, or confluent erythema. The bullous lesion may rupture and lead to other lesions. (5)

Case presentation:

The patient, aged 14, has been followed since the age of 9 for juvenile myoclonic epileptic seizures, initially put on valproic acid associated with carbamazepine, a brain CT scan without injection was done and returned without abnormalities.
Despite this treatment, the patient continued to suffer from convulsive seizures, requiring her to be hospitalized several times in hospital facilities for treatment.
A month and a half before we received her in our structure, the patient consulted a neurologist who requested an electroencephalogram, which returned in favor of a single generalized paroxysmal discharge associated with some discharges in the occipital as well as in the right middle temporal and in the left middle posterior temporal. Following these results, the patient was put on LTG.
A prescription protocol of: 1 tablet per day of 25 mg for one week, then 2 tablets per day of 25 mg for one week then 3 tablets per day for one week and at the end 4 tablets per day.

Symptoms began at the end of the 2nd week after the initial dose of LTG, with conjunctival hyperemia, bilateral purulent discharge and general malaise. His parents gave him an antihistamine and protected amoxicillin without any improvement. Symptoms progressed to localized dermatosis and edema on the face and mouth, ulcers of the oral mucosa. Non-painful, pruritic erythematous macules were observed in the anterior and posterior thorax andupper limbs, then the dissemination of lesions to the body. Due to the worsening of symptoms, the patient was transferred to the emergency room of our structure.

On admission, his face presented with palpebral edema and erythema. The anterior and posterior thorax presented erythematous, violaceous and polymorphic plaques of different sizes with a tendency to merge. Scratching lesions were observed with diffuse scales on both sides of the upper limbs.
The patient presented with low blood pressure: 50/30 mmHg, hence the management as anaphylactic shock: large caliber IV line, vascular filling with isotonic saline 0.9% associated with 2 boluses of 10 micrograms of adrenaline, elevation of the lower limbs, nebulization with salbutamol and atrovent.



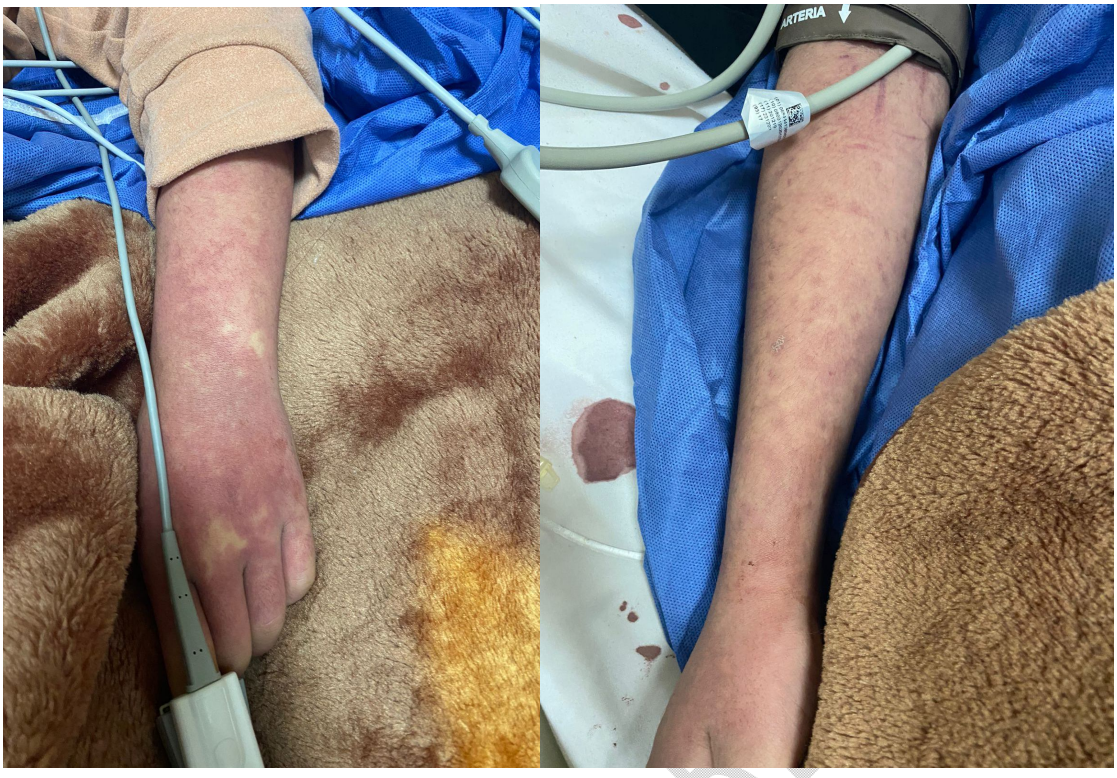


Fig1: Patient transferred to the emergency room due to the worsening of symptoms

The evolution is marked by stabilization on the hemodynamic and respiratory levels.
The affected mucocutaneous surface was <10%; therefore, the diagnosis of SJS was made.
The initial results of the basic laboratory examination (blood count, blood ionogram, hemostasis assessment, liver and kidney assessment) demonstrated: hyperleukocytosis at 30090 with lymphocyte predominance at 53.5%.
A CRP at 16.8, a disturbed liver function test: (ALAT (275U/L) 6 times normal and ASAT (317 U/L) 7 times normal) and gamma GT at 212 U/L (normal 0-40U/L).

Fluid management and intravenous (IV) administration of methylprednisolone (1 mg/kg/day for five days).
The patient refused to have a skin biopsy performed.

During the first 72 hours after admission, the patient remained stable.
A saline and soap wash for skin lesions.
During hospitalization, his symptoms and skin lesions and his laboratory assessment improved.

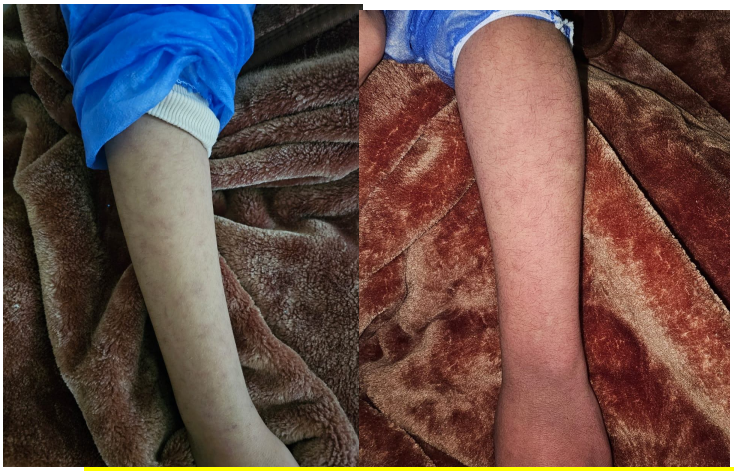


Fig 2 :Improvement of patient's skin lesion conditionduring hospitalization

Discussion:

Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis:

SJS was first defined by Albert Stevens and Frank Johnson in 1922 (7). These drug eruption events are rare, with an estimated overall incidence of 1.2 to 6 cases per million population per year for SJS (8). In the pediatric population, Hsu et al. reported an incidence rate of 5.3 and 0.4 cases per million children for SJS and TEN in the United States, respectively (9).

The diagnosis of NETs is essentially clinical. Digital photographs should be taken to monitor the evolution of lesions in the acute phase.
The clinical examination must also include questioning [age, autonomy, history of drug allergy, comorbidities and active cancer,immunosuppression, etc.],vital signs [temperature, blood pressure, pulse, respiratory rate, oxygen saturation, weight). The larynx is less commonly affected in TEN than the oral cavity or oropharynx, but its involvement is often associated with tracheobronchial lesions, hence the high risk of respiratory complications. Skin biopsy confirms the diagnosis and excludes autoimmune bullous dermatosis. The diagnosis of NETs should not be delayed by waiting for histological results.

Pathophysiology:

The pathophysiology of SJS is based on complex immunological mechanisms, mainly linked to delayed-type hypersensitivity.

a) T lymphocyte activation:

SJS is primarily associated with a T-cell-mediated hypersensitivity reaction. This activation occurs when drugs or other agents are perceived as strange by the immune system. Cytotoxic T lymphocytes (CD8+) recognize the altered epithelial cells and induce their apoptosis, leading to destruction of the epidermis. (10-11)

b) Cytokines and inflammatory mediators:

During this reaction, T lymphocytes release pro-inflammatory cytokines, including granulysin and TNF-alpha. These cytokines amplify inflammation and increase vascular permeability, contributing to the infiltration of immune cells into skin tissues. Granulysin, in particular, is involved in the lysis of keratinocytes and plays a key role in the apoptosis process. (12)

c) Roles of FAS receptors:

Another important mechanism is the interaction between the FAS receptor (CD95) and its ligand (FASL), which also leads to apoptosis of epithelial cells. This apoptotic pathway is often activated in drug reactions, contributing to blistering and skin peeling. (13)

Assessment to be requested:

When evaluating Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), a complete blood count is crucial to diagnose and manage these serious conditions.
Recommended tests include:
A complete blood count, a blood ionogram, a renal assessment: urea creatinine, a liver assessment: ASAT, ALAT, Gamma GT, monitoring of blood sugar, CPR, PCK and LDH, prothrombin level, and lactate measurement.
These tests not only allow to assess the general condition of the patient but also to identify specific abnormalities that could indicate an increased severity of the syndromes. (6)

What about lamotrigine?

LTG is an antiepileptic drug that is also used as a mood stabilizer. (14)
Side effects of LTG as mentioned in the leaflets (15):

- Very common (more than 10% of people): headache, mild skin rash.
- Common (1 to 10% of people): drowsiness or insomnia, dizziness, irritability, tremors, agitation, diarrhea, nausea, vomiting, dry mouth, joint or back pain, feeling tired.
- Uncommon (less than 1% of people): lack of coordination, double or blurred vision, hair loss, photosensitivity.

Stevens-Johnson syndrome has also been mentioned as a hypersensitivity reaction/rare side effect in the LTG package insert characterized by severe rash, fever, lymphadenopathy, liver dysfunction, blood disorder and disseminated intravascular coagulation with multiorgan dysfunction.
It has also been suggested that rapid increases in LTG dose increase the risk of rash. (16)
In our case, the patient had been on valproic acid for years and had no side effects suggesting a drug reaction. A discontinuation of this treatment for several weeks preceded the taking of LTG.
Rapid dose escalation is usually associated with an increased risk of cutaneous side effects, and in our case the dose escalation was 25 mg once daily for one week, followed by 50 mg once daily for one week, and then increased to 75 mg once daily. All of her symptoms appeared after about two weeks of LTG treatment.
In our case, symptoms started two weeks after taking LTG, which is the expected time when these reactions usually appear (first eight weeks). The lesions did not progress and symptoms improved after stopping LTG.
Diagnosis is clinical, using three elements as a guide: cutaneous manifestations, mucosal changes and histopathological results of skin biopsy (17).
In our case, the parents refused the biopsy.
We report this case because LTG is increasingly used in psychiatry (especially as a mood stabilizer) and because of the rarity of Stevens Johnson syndrome (SJS) as an adverse effect of LTG.
The mechanisms of LTG-induced SJS are less well understood, but recent evidence suggests that antiepileptic drug-related hypersensitivity may be a consequence of chemotoxic and immunological injury; however, the pathogenesis of this reaction may vary somewhat among different antiepileptic drugs. (18)

The risk of developing Stevens-Johnson syndrome with LTG is rare and relatively predictable within the first few weeks of use; however, clinicians prescribing this drug should be aware of this high-risk condition. Current data indicate that although LTG can cause a serious rash for which clinicians should continue to adhere to new standard dosing paradigms and practical

precautions, in the case of a non-serious rash, readministration of LTG may also be considered 20 in many cases.

Conclusions:

In conclusion, hypersensitivity reactions constitute a risk during the administration of lamotrigine, clinical monitoring must be close during the first 8 weeks, this period remains critical since it is at this time that possible complications of treatment develop.
As for the pediatric population, family members should be informed of this possibility and ensure the clinical monitoring of their child.
Stevens-Johnson syndrome is a life-threatening condition that requires immediate intervention and a multidisciplinary approach.

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