Case report

STEVENS-JOHNSON SYNDROME –TOXIC EPIDERMAL NECROLYSIS induced by LAMOTRIGINE in a 15-year-old girl: A 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. TEN and SJS are important adverse drug reaction in dermatology and medicine department. For better patient care and reduce burden to patients effective reporting of ADRS are necessary. Effective reporting also affect on reducing mortality and morbidity. This study is scientifically sound.
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.

Abbreviations: SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; EN :epidermal necrolysis; BSA: body surface area; LTG: Lamotrigine; ADRS: Adverse drug reactions

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 TEN 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.

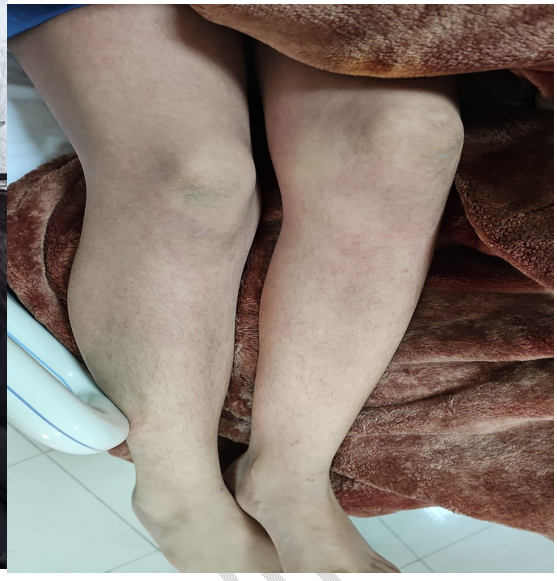
Rarely, occurrences of anticonvulsant-induced SJS and TEN have started in infancy or early childhood, although the majority have been documented in young adults and after puberty. (4) Significant involvement of the skin and mucous membranes of the mouth, nose, eyes, vagina, urethra, gastrointestinal tract, and lower respiratory tract are among the clinical characteristics of SJS. Within 4 to 28 days (up to 56 days) of drug use, which is typically the first time in life, drug-induced lesions develop and persist as eruptions for 2 to 3 weeks. (6)
Initially appearing as macules, the rash may progress into confluent erythema, urticarial plaques, papules, vesicles, or bullae. Other lesions could result from the bullous lesion rupturing.(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.

Conjunctival hyperemia, bilateral purulent discharge, and general malaise were the first symptoms to appear at the end of the second week following the first dose of LTG. Without any improvement, his parents administered amoxicillin and an antihistamine. The symptoms developed into oral mucosal ulcers, regional dermatosis, and facial and oral edema. Before the lesions spread over the body, non-painful, itchy erythematous macules were seen in the upper limbs and anterior and posterior thorax. The patient was moved to our building's emergency room since their symptoms were getting worse.

His face had erythema and palpebral edema when he was admitted. Erythematous, violaceous, and polymorphic plaques of varying sizes with a propensity to coalesce were seen on the front and posterior thorax. On both sides of the upper limbs, scratching lesions with dispersed scales were seen.
The patient presented with low blood pressure: 50/30 mmHg, hence the management as anaphylactic shock: large caliberIV 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.



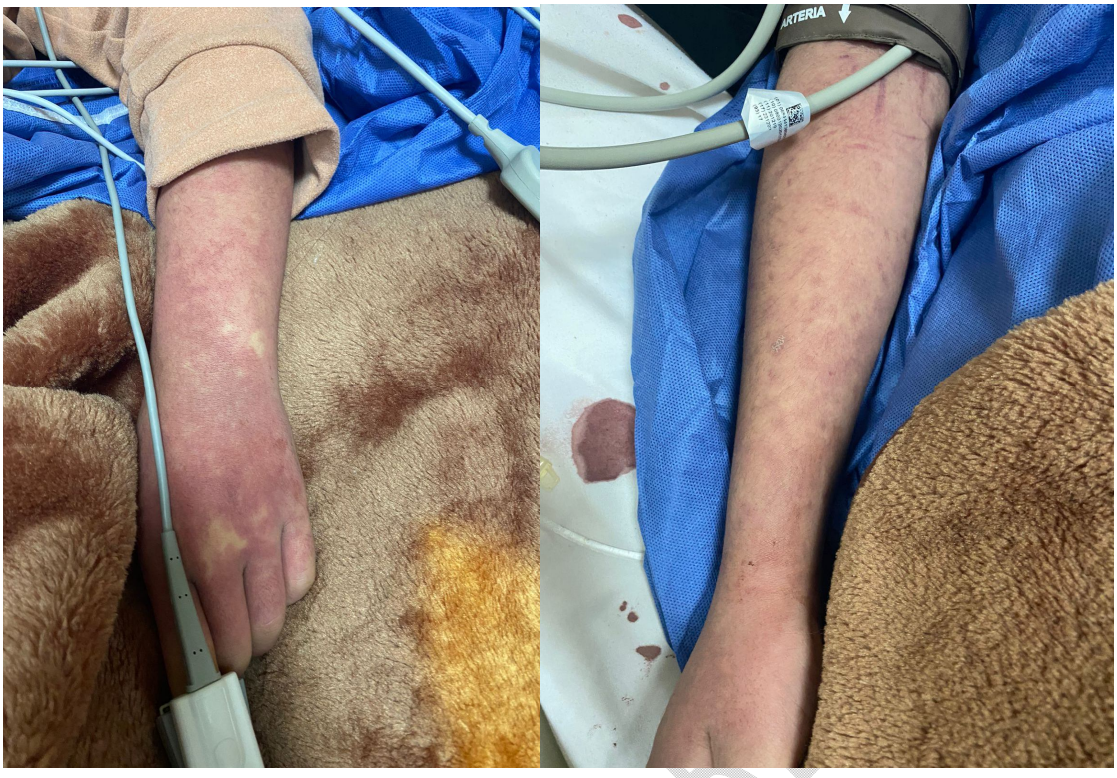


Fig1: Patient transferred to the emergency room due to the worsening of symptoms

Stabilization at the respiratory and hemodynamic levels characterizes the evolution.
Since less than 10% of the mucocutaneous surface was impacted, SJS was diagnosed.
Hyperleukocytosis at 30090 and lymphocyte predominance at 53.5% were the first findings of the basic laboratory test (blood count, blood ionogram, hemostasis assessment, and liver and kidney assessment).
A disrupted liver function test with a CRP of 16.8, gamma GT of 212 U/L (normal 0-40U/L), and ALAT (275U/L) six times normal and ASAT (317U/L) seven times normal.

Methylprednisolone (1 mg/kg/day for five days) administered intravenously (IV) along with fluid management.
The patient declined to get a skin biopsy.

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.

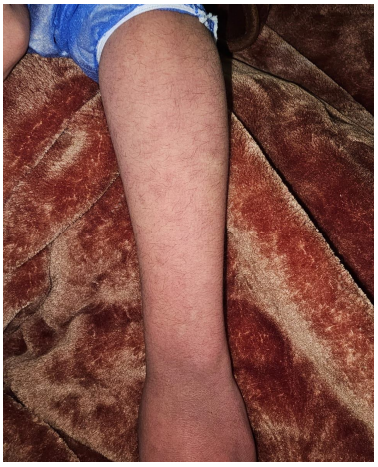


Fig 2:Improvement of patient's skin lesion conditionduring hospitalization

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).

TENs are primarily diagnosed clinically. During the acute phase, digital photos should be taken to track the lesions' development.
Vital signs (temperature, blood pressure, pulse, respiration rate, oxygen saturation, weight), as well as questions about age, autonomy, history of drug allergies, comorbidities, active cancer, immunosuppression, etc., must be part of the clinical examination. Although the larynx is not as frequently damaged by TEN as the oral cavity or oropharynx, it is frequently linked to tracheobronchial lesions, which increases the risk of respiratory problems.
A skin sample rules out autoimmune bullous dermatosis and validates the diagnosis. Waiting for histology results should not postpone the diagnosis of TENs.

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.

According to the LTG package insert, Stevens-Johnson syndrome is a rare side effect or hypersensitivity reaction that manifests as severe rash, fever, lymphadenopathy, liver failure, blood problem, and disseminated intravascular coagulation with multiorgan malfunction. Rapid increases in LTG dosage have also been proposed to raise the risk of rash. (16)
In our instance, the patient had been using valproic acid for years without experiencing any adverse effects that would indicate a medication reaction. Prior to starting LTG, this treatment was stopped for a few weeks.
In our situation, the dose escalation was 25 mg once day for one week, followed by 50 mg once daily for one week, and finally increased to 75 mg once daily. Rapid dose escalation is typically linked to an increased risk of cutaneous adverse effects. After receiving LTG for almost two weeks, all of her symptoms manifested.
In our instance, symptoms began two weeks after taking LTG, which is inside the first eight weeks, which is when adverse reactions are often predicted to manifest. After quitting LTG, the symptoms improved and the lesions did not worsen.
Three factors—cutaneous symptoms, mucosal alterations, and skin biopsy histological results—are used to guide the clinical diagnosis. (17)
In our instance, the biopsy was declined by the parents.
We record this case because Stevens Johnson syndrome (SJS) is an uncommon side effect of LTG and because LTG is being utilized more and more in psychiatry, particularly as a mood stabilizer.
Less is known about the mechanisms underlying LTG-induced SJS, but new research indicates that immunological and chemotoxic damage may be the cause of antiepileptic medication-induced hypersensitivity; the pathophysiology of this reaction may change slightly among antiepileptic medications. (18)

Although there is a small and predicted chance of getting Stevens-Johnson syndrome during the first few weeks of using LTG, doctors who prescribe this medication should be aware of this high-risk illness. According to current evidence, readministration of LTG may be considered in many situations when the rash is not severe, even if it can create a major rash for which doctors should continue to follow new standard dose paradigms and practical measures.

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.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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