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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/15412
DOI URL: http://dx.doi.org/10.21474/IJAR01/15412

RESEARCH ARTICLE

STEVEN JOHNSON'S SYNDROM ON LAMOTRIGINE

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Manuscript Info

Manuscript History
Received: 18 July 2022
Final Accepted: 20 August 2022
Published: September 2022

Key words:-
Lamotrigine, Bipolar Depression, Steven Johnson's Syndrom

Abstract

Introduction: Lamotrigine is an anti-epileptic drug indicated for the treatment of bipolar disorder and recurrent depressive disorders. Its efficacy has been demonstrated. However, its use may be limited by the risk of severe, life-threatening allergic reactions.

Objectives And Methods: We report hereafter the clinical case of a patient suffering from bipolar depression treated with lamotrigine which induced skin allergies in her. Our objective will be to detail the rules of prescribing the treatment, to describe Steven Johnson syndrome, a serious adverse effect to lamotrigine, to discuss the urgent course of action in the event of severe allergic reactions to lamotrigine as well as the therapeutic options after a hypersensitivity reaction to lamotrigine.

Clinical Vignette: This is a patient followed in psychiatry for bipolar disorder, put on esitalopram clomipramine, aripiprazole and Lamotrigine, who was admitted to dermatology for minimal erythematous maculo-papular rash on the face and limbs with involvement of the oral and genital mucosa; appeared 4 weeks after introduction of lamotrigine.

Conclusion: Despite the efficacy of lamotrigine as an effective mood regulator in the treatment of recurrent depressive episodes and depressive episodes in bipolar disorder, this antiepileptic drug must be used with caution to avoid serious life-threatening reactions.

Introduction:-

Lamotrigine (LTG) is an anticonvulsant approved by the Food and Drug Administration for Lennox-Gastaut syndrome, for partial seizures, tonic-clonic seizures, and maintenance treatment of bipolar disorder [1]

In bipolar disorder, it is one of the most proven medications for the treatment of depression, according to several evidence-based guidelines[2-5]

Rash is a common side effect of LTG treatment, occurring in 8.3% of cases, half of whom withdrew their medication as a result.

Anticonvulsant hypersensitivity syndrome is clinically manifested by maculopapular exanthema, fever and lymphadenopathy.

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Simple maculopapular exanthems related to lamotrigine are seen in up to 10% of users and are mainly observed during the first 8 weeks of treatment.

Several cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been described in patients taking this drug, especially when titrating too rapidly at initiation of treatment or when sodium valproate is used concurrently. The risk of severe LTG-related rash is reduced by more than 10-fold with a slow titration schedule, such as fortnightly increases of 25 mg [6].

Lamotrigine can also cause hepatic, renal, haematological and pulmonary disorders [7]

A genetic predisposition has been identified for certain ethnic groups. [8-10]

Other risk factors for LTG-induced hypersensitivity include human immunodeficiency virus (HIV) infection, coadministration of antiviral drugs, liver disease, advanced age and concomitant use of immunosuppressive agents[8-11].

Method:-

We studied a clinical file of a child hospitalized in the dermatology department of the Avicenne hospital where a psychiatric opinion was requested.

We collected the clinical data, the history of the disorder and the therapies as well as the evolution through the patient's file in the dermatology department as well as the psychiatric interviews with the patient and her family.

Clinical Vignette

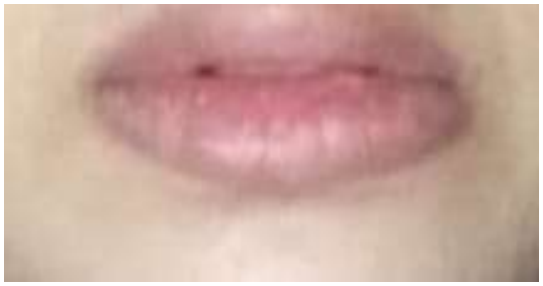
This is a 16 year old patient, followed in psychiatry for bipolar disorder.

The history of the disease seems to date back to 2017 with the occurrence of a manic episode followed by several depressive episodes.

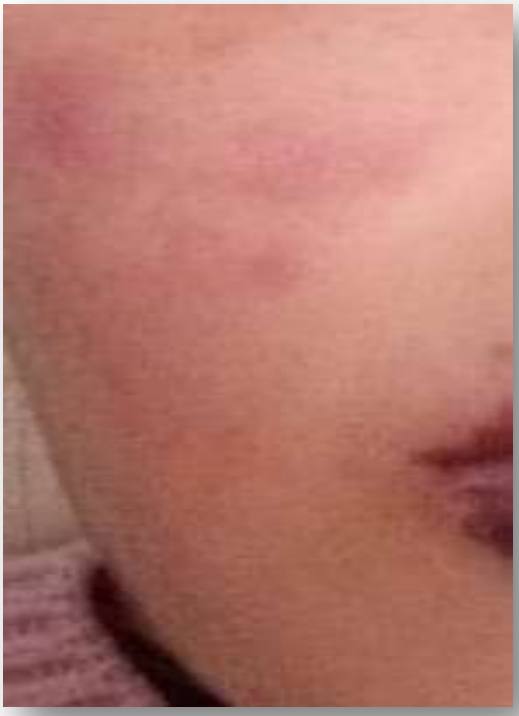
In 2021, she was started on Lamotrigine with progressive dose escalation. Initially, the patient was taking 25mg/d for 7 days then 50mg/d for 7 days then 75mg/d for 7 days then 100mg/d.

The patient presented 4 weeks after initiation of lamotrigine and one day after the dose increase to 100mg/d with an acute mucocutaneous rash.

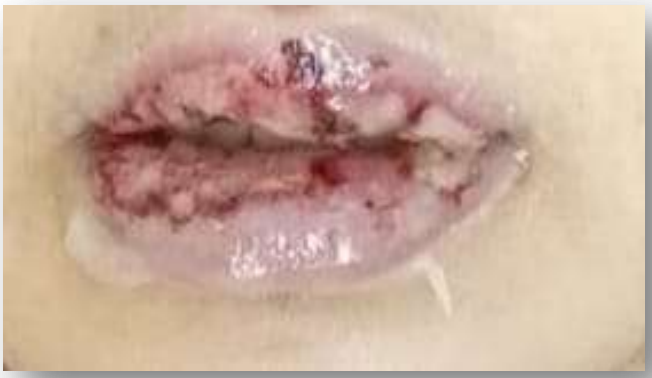
She developed edema of the lips and tongue with cheliitis fumiginosa and painful erosions of the oral mucosa.



2 days later, she presented with a minimal, non-pruritic, erythematous maculo-papular rash, initially on the arm, then the thighs, then the face.



The patient subsequently stopped lamotrigine. However, there was an extension of the painful lesions to the oropharyngeal mucosa with hypersialorrhoea and dysphagia, to the conjunctival mucosa and to the genital mucosa causing burning during urination.



It is worth noting that the patient's condition was apyrexic and preserved, without any notion of arthralgia, cough or flu-like syndrome.

Given this clinical picture, the patient was admitted to dermatology.

The physical examination of this patient revealed a weight of 60 kg, a height of 159 cm and a BMI of 23, a GCS of 15, a heart rate of 100 beats per minute and a respiratory frequency of 16 cycles per minute.

The dermatological examination revealed :
On the skin :
- A few erythematous macules on the face and left helix
- Presence of small papules, some of which are eroded, on the thighs and upper limbs, including the palms

- Negative Nikolsky's sign
- Less than 10% of skin surface affected
- No cocoon lesion
- Several hyperpigmented scars all over the body
- Benign looking nevi

Mucosal :
- Fumiginous cheliitis limiting mouth opening
- Depilated tongue
- Erosions of the endo-buccal mucosa: palate and inner cheeks
- Involvement of the conjunctival mucosa with sticky secretions
- Erosions on the vulva

In the area of the phanera :
The scalp was the site of an occipital erythematous scaly patch with no nail or finger abnormalities.

A diagnosis of Steven Johnson syndrome was made in view of the high risk of skin allergy to lamotrigine, the involvement of less than 10% of the skin surface, the involvement of mucous membranes and a concordant delay of 4 to 28 days.

The therapeutic course of action was to hospitalise the patient in dermatology with cessation of lamotrigine and declaration to the pharmacovigilance centre, a hypercaloric and hyperprotic diet, a shower every 3 days with soapy water and local care: eye care, mouthwash, gargle with prednisolone, and placing compresses with officinal vaseline between the lips and on the vulva.

An ophthalmic opinion was requested and found a normal corneal examination, negative fluorescence, alterations of the conjunctival mucosa on the free edges of the eyelids, in particular the upper left one, with no inflammation of the anterior segment.

She was put on ofloxacin eye drops 4/D, dexafree 3/D and physiodose lavage

A 48-hour check-up noted an improvement in the mucoconjunctival lesions

A check-up was also done showing a normal NFS, ionogram, albumin, ferritin, a CRP increased to 133, negative viral serologies and a normal radiothoracic

A psychiatric opinion was requested.

The psychiatric interview of the day had found a patient who was calm on the motor level, with good body care, her mimicry was hypomobile, contact with her was easy but superficial, her speech was normal in its course and continuity, her basic activities were preserved: she was a patient who was conscious, well oriented in time and space, attentive with a memory that seemed to be preserved. Her thinking was characterised by ideas of low self-esteem, with no thoughts of suicide or homicide. There were no perceptual or judgmental disturbances. His mood was depressed with mood congruent affect. Her appetite was preserved but it was difficult for her to eat normally given her oral lesions with sleep insomnia and normal sexuality.

This was a patient who had been diagnosed with bipolar disorder: current characterized depressive episode, and was being put on Lamotrigine, Aripiprazole, Escitalopram and Clomipramine.

Lamotrigine and Aripiprazole were discontinued with the addition of Quetiapine to the antidepressants.

The evolution was favourable with no new lesions or fever.

The patient was therefore discharged from the dermatology department and referred to the psychiatry department for further follow-up.

Discussion:-

Lamotrigine: Prescription Protocol

Several guidelines recommend the use of lamotrigine in bipolar depression as first line of treatment, or as second line. However, one of the main concerns with the use of lamotrigine is the risk of a life-threatening rash (e.g. Stevens-Johnson syndrome or toxic epidermal necrosis).

This risk is reduced by slow titration to the target dose of 100-200mg/d:

- first 2 weeks: 25mg/d
- 3rd and 4th week: 50mg/d
- 5th and 6th week: 100 mg/d
- From week 7 onwards: 200 mg/d

Our patient benefited from a slow titration protocol with the use of 25mg/d for 7 days, 50mg/d in the 2nd week, 75mg/d in the 3rd to reach 100mg in 4 weeks.

Steven Johnson Syndrome

Stevens-Johnson syndrome (SJS) is a hypersensitivity event associated with a mortality rate of up to 10% due to sepsis[11].

It usually occurs between the 5th day and 8th week of lamotrigine administration, due to the time required to activate the body's immune response; however, cases of SJS have been reported after 6 months of lamotrigine administration. [12,13]

Patients who develop SJS may initially present with flu-like symptoms, followed by painful red or purple rashes characterised by generalised erythema, necrosis and bullous detachment of the epidermis and mucosa

These eruptions classically develop on the face and upper torso.[14]

Our patient did not initially present with an influenza-like syndrome, nor did she have torso involvement. She had oral, genital and conjunctival mucosal involvement with a painful rash on her face and arms.

Skin Rash: The Question Of Rechallenge

Neurologists and psychiatrists have an obligation to educate their patients about adverse events and may receive messages from their patients about a rash after initiation of an anticonvulsant such as lamotrigine.

If symptoms have started within 8 weeks of the first dose and other causes (co-medication, chemical/cosmetic contact, known or new skin conditions) have been considered and excluded, it is important to characterise the rash:

When it is haemorrhagic, pustular vesicular, confluent or involving mucous membranes, the risk of a severe allergic reaction is high, which was the case in our patient.

If the rash is non-confluent, maculopapular, limited to the skin and occurs in a generally healthy patient, it is usually mild and the dose of the anticonvulsant involved can be reduced and the patient monitored. If necessary, an antihistamine may be started. After resolution of symptoms, the dose may be increased at a slower rate.

Serious cutaneous adverse reactions to lamotrigine are rare, with only 0.3% of those with a rash requiring hospitalisation. Nevertheless, resumption of lamotrigine therapy should only be attempted if the patient can be safely monitored in the community and the benefits of continued treatment outweigh the risks. [15]

On the other hand, after the onset of SJS/TEN, DRESS syndrome, resumption of treatment should not be attempted. Therefore, the use of lamotrigine was contraindicated in our patient.

Bipolar Depression: What Alternatives?

The combination of olanzapine and fluoxetine remains the most effective treatment for bipolar depression according to the Maudsley guidelines. However, its use is limited by the metabolic side effects of olanzapine. [16]

First-line alternatives include quetiapine, olanzapine, lurasidone, lamotigine, and valproate. Lithium is effective but evidence for its efficacy is weak. [17]

In our clinical vignette, quetiapine was chosen as an alternative to lamotrigine, due to the high metabolic and cardiovascular risk of olanzapine, represented by the patient's weight as well as a family history of diabetes, hypertension and sudden death of the grandfather.

Conclusion:-

Lamotrigine is an anticonvulsant with proven efficacy in bipolar depression. However, the risk of rashes which can be severe limits the prescription of this drug in some patients. Slow titration, patient psychoeducation and prompt management of complications are necessary for patient safety.

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