Toxic epidermal necrolysis in an adolescent diagnosed with bipolar disorder II and treated with Lamotrigine

Jamie Rodríguez L.[1,2], María Elena Zegarra S.[3,4], Lizardo Cruzado[1,3]

Toxic epidermal necrolysis is a severe skin disease, most often triggered as an adverse drug reaction, with high morbidity and mortality. Lamotrigine, along with other mood stabilizer drugs, is the most frequent drug causing this complication, which consists of necrosis and detachment of the epidermis and mucosa in more than 30% of the body surface, with consequent loss of water and electrolytes, systemic inflammatory response, susceptibility to infections and even sepsis, in addition to other possible ominous sequelae. Currently, the diagnosis of bipolar disorder is made more frequently, including the age group of children and adolescents, but such a diagnostic process is characterized by difficulties and controversies to a greater extent than other psychiatric diagnoses. This requires a comprehensive diagnostic process and pharmacological selection, with full knowledge of the molecules in the drug arsenal so, in case of Lamotrigine prescription, a strict psychoeducation for patients and their family members should be made, as well as a strict and close follow–up. With respect to the case of an adolescent girl diagnosed with bipolar II disorder, who received Lamotrigine during a depressive episode, but with an inappropriate posology, and she developed toxic epidermal necrolysis, we reviewed and commented on the corresponding literature. We concluded that extreme caution is necessary when deciding the use of Lamotrigine to minimize the risk of this severe adverse effect.

Key words: *Lamotrigine; Stevens–Johnson Syndrome; Bipolar Disorder. (Source: MESH–NLM)*

INTRODUCTION

The skin is the most frequent target of Adverse Drug Reaction (ADR). Nearly a third of them attack this organ[(1)]. The WHO (World Health Organization) defines as ADR any unintended harmful effect of a drug used in human beings with proper dosage for the treatment or prevention of a disease; Severe ADR is that requiring hospitalization or long hospital stay, causing persistent/significant disability, which threatens the life or that causes death[(2)]. In psychiatric medication, anticonvulsants/mood stabilizers are those having a higher incidence of severe skin ADR, even above non–steroidal anti–inflammatory antibiotics, which are the most associated groups, in descending order of frequency[(3)].

Toxic epidermal necrolysis (TEN) was described by Lyell in 1956 and it is the most seve-

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1 National Institute of Mental health “Honorio Delgado Hideyo Noguchi”. Lima, Peru.
2 Universidad Nacional Mayor de San Marcos. Lima, Peru.
3 Universidad Peruana Cayetano Heredia. Lima, Peru.
4 Hospital II–1 de Moyobamba. San Martín, Peru

re cutaneous ADR, as its mortality rate ranges between 30 to 50%. It consists of spread apoptosis of keratinocytes in the context of an immune late hypersensitivity response, mediated by cells associated to some histocompatibility antigens, leading to development of wide and numerous brittle blisters on the skin and mucosa areas and when these open, wide areas of the skin are exposed, thus getting a massive loss of interstitial fluid and electrolytes, exposure to multiple infections and sepsis, apart from other severe complications[4.5]. There are several other severe ADRs, with typical blisters, which were classified by consensus in 5 groups: erythema multiforme bullosum, Stevens–Johnson syndrome (SJS), overlapping syndromes SSJ–TEN; in turn TEN has two varieties: with/without purple erythema (spots). SSJ and TEN are deemed as the ends of the same clinical picture. The NET describes that the percentage of body surface affected is massive, and it is always above 30%. Its incidence is 0.4 to 1.9 cases per million of inhabitants, per year, although along with its linked pathologies (SSJ SSJ–TEN) reaches 2 to 7 cases per million of inhabitants, per year. It is slightly more frequent in women than in men, with a relationship of 1.7 to 1; likewise it has a higher incidence at early age, rather than with 80–years–old elderly people. Asian ethnic ancestry has a double risk than caucasian groups[6.7]. Other risk factors are infection caused by HIV, neoplasias, autoimmune diseases, acute renal disease, drugs consumption with addictive risk, such as Alopurinol, other antiepileptic drugs, antibiotics, etc.[8]

Lamotrigine was approved in Europe, USA in the 1990s, as a treatment for complex partial/general epilepsy. Its action is to reduce release of glutamate, and at the same time, modulate reuptake of serotonin and dopamine. In the psychopharmacological scope, it was approved by the USA Food and Drug Administration as a maintenance treatment for Bipolar disorder I, although it is "off–label" tagged as a coadjuvant treatment in major bipolar depression, schizophrenia, schizoaffective disorder, impulse control disorders and borderline personality disorder, among other disorders[9].

One of the most complex topics in current psychiatry is diagnosis of Bipolar affective disorder (BPAD), specially for bipolar disorder type II, even more in children adolescents population. If at the beginning an under diagnosis of BAD was claimed[10], later the opposite was reported: an over diagnosis of this pathology, with an blurred arising and extremely encompassing "bipolar spectrum", that even though it may have some advantages from a research point of view, it has some disadvantages in clinical practice, as it exposes people to unnecessary medication and to the stigma of an incorrect diagnosis[11]: BAD is a very controversial topic, up to a point where currently even deletion of BAD type II is being proposed[12, 13], but there is no consensus about the right treatments. In this sense it is quite relevant to review the topic of Lamotrigine being prescribed to an adolescent with an alleged diagnosis of BAD II, which caused the severe ADR, topic of this report.

Clinical Case

The patients is a 20–year–old woman. She is single and has no children, and is from Lima. She is half blood. She is a college student and comes from a nuclear family. She is the eldest of three siblings. She had a febrile convulsion when she was two years old. She had typhoid fever when she was 5 years old and had enuresis till she was eleven years old. One and a half month before developing TEN she had chickenpox.

Since she was 13 years old, her mood started to have predominance of dysphoria, boredom, and emptiness feelings, along with intermittent suicidal ideation. She reported sadness, as she felt alone and did not get good marks at school. Apart from that she experienced shyness, and rejection to social interaction. She also had conducts of trichotillomania, and self aggression (shallow cuts on her forearms). She was under psychiatric treatment, and was diagnosed with major depression and social phobia: she was prescribed with Sertraline, till progressively reaching 100 mg, per day, apart from family therapy. She felt a bit released from her symptoms. After one year and a half, due to the full remission of her conditions, she was gradually eliminating her medication.

When she was 15 years old, and after six months with no psychiatric medication, she had to go back to the psychiatric room, as she

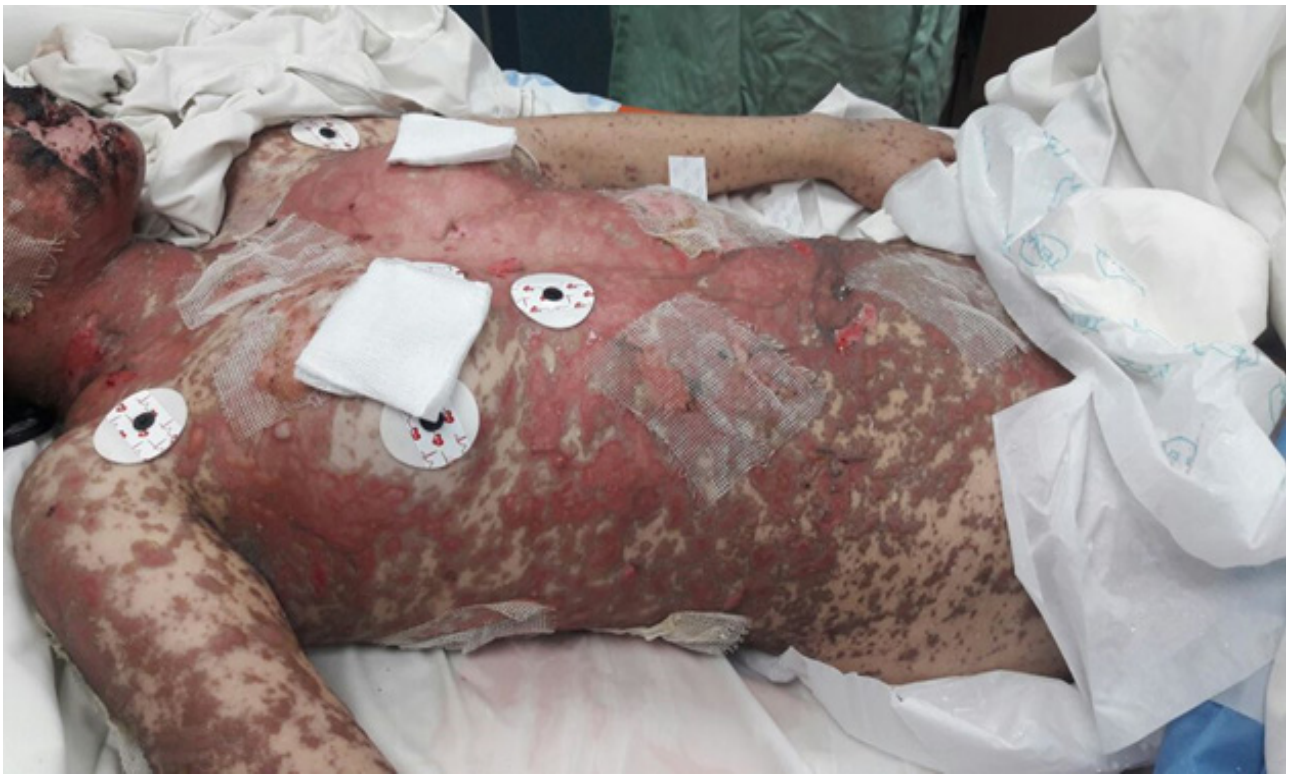
cut her forearms again. She had a sad/irritable mood, with apathy, anhedonia, she did not participate in school activities and had one suicidal attempt with an overdose of 20 mg of Clonazepam. She even quit school, but she finally passed the year. She resumed her treatment with Sertraline, which increased to 100 mg per day. There was a partial progressive improvement. After three months and during the next year she went to her consultation just a couple of times, as she seemed to be stable: the family reduced her dosage and removed her medication –after 10 months– due to gastrointestinal conditions, although she was in good conditions: she even resumed her accounting studies at an Institute.

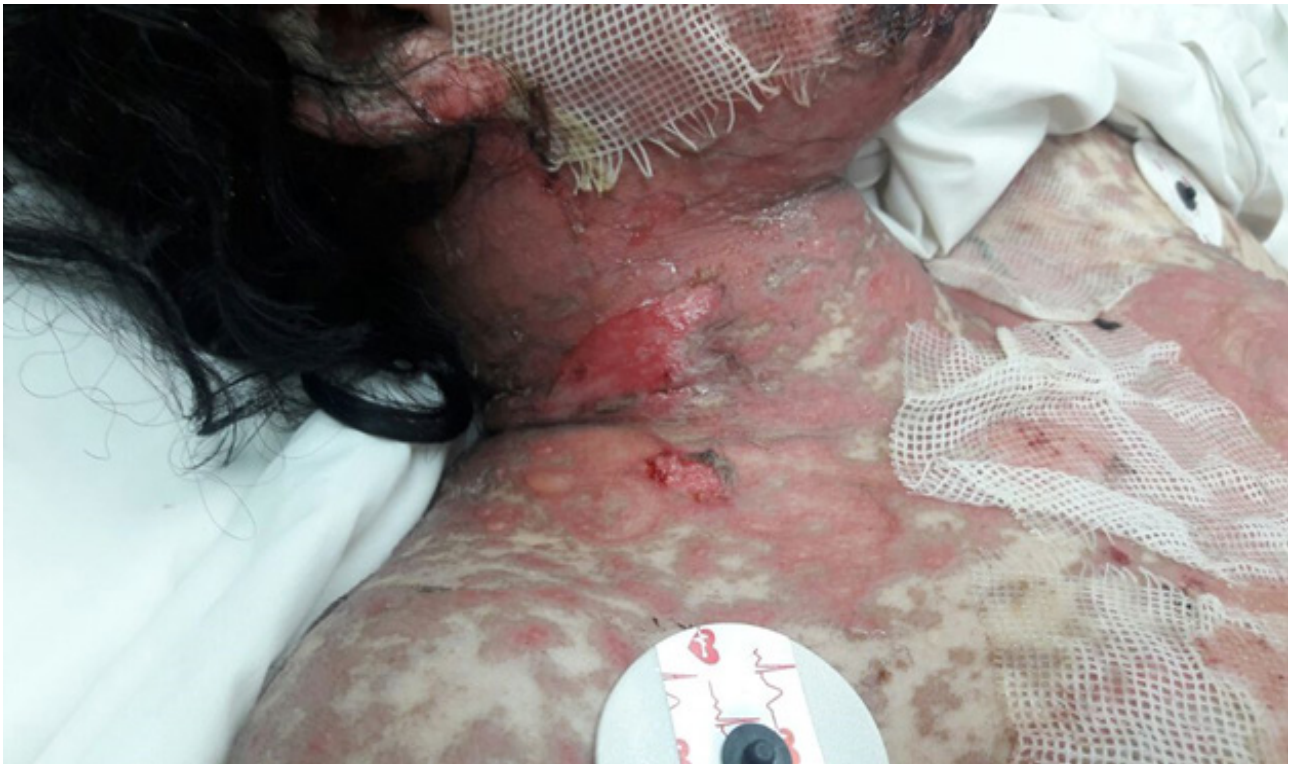
When she was 17 years old, she went back to her consultation. Her main disorder was social anxiety: she quit school when she had a presentation in front of her peers. She only dressed in black, she cried very often and sometimes she cut her abdomen; when she remembered people who had mocked at her, she stabbed her mattress with a knife. She restarted her treatment with Sertraline and she seemed to feel released of her conditions, but it was only for a brief period, as after a few months she reported that three times a week she felt so bad that she did not even get up from her bed. Although this conduct was intermittent and she had other days when she felt happy, with energy, and she needed to sleep less. That was happening for about a year. Based on this information her diagnosis was hypomania and bipolar affective disorder, type II: she was prescribed with Lamotrigine, with a dosage of 50 mg per day. Simultaneously she continued with Sertraline, 75 mg per day. After one week she had a control and reported to suffer migraines. She was listlessness, she denied to have suicidal ideas; she remembered painful moments of her school life and cried: her dosage was increased to 100 mg per day of Lamotrigine.

After 16 days she was prescribed with Lamotrigine, the patient went to Psychiatric Emergency as she suffered slightly moderate olecranon migraine, which started nearly the second day of Lamotrigine intake and it was increasing. On the fifth day she had two maculoerythematous spots on her right malar area. On day 12 she had her lips numb. At the Emergency Room she also had eye pain, conjuntival injection and dacriorrea, apart from odinofagia for solids and liquids –which started on day 13–. When she was physically examined she had a punctiform erythematous macular eruption on both cheeks, and scarce vesicular lesions on her lower limbs. At the Health Center she was diagnosed with faringitis and was prescribed with Amoxiciline, Ibuprofen and Gentamicin eye drops the previous day. From the Psychiatric Emergency she was referred to the Emergency Room of the General Hospital where she was only prescribed with spray Gingisona, but she returned after two hours as she had sphacelous of the labial mucosa, sialorrhea, increasing macular eruption on her thorax and face, itchy skin, and high eye irritation, apart from fever, 38° C. She was admitted at the hospital and her psychiatric medication was ceased. That same day she was at the Intensive Care Unit. She remained there for 18 days. She had cutaneous sphacelous all over her face, neck, trunk, proximal are to her upper/lower limbs, within one week. She was under treatment advanced life support, antibiotic prophylaxis, corticotherapy and gamma globulin therapy. She was also in the surgical room four times, for surgical débridement and artificial skin grafting (bovine–origin dermoepidermal substitute) on the anterior/posterior areas of her thorax. (Images 1–2).

When she was discharged, she had persistent lesions in oral mucosa and eye sequelae (dry eye syndrome and photophobia), which required topical, oral and ophthalmic medications, apart from hypochromic/hyperchromic maculae on several parts of her body. From the week after her hospital discharge she was supported by the Psychiatric Emergency several times, as she remained dysphoric and concerned about the her TEN sequelae. She had self injuring/suicidal impulses, that is why she used to remain under observation at the Emergency Room. Finally, she accepted to resume her psychopharmacotherapy and she was progressively improving, after three months with Sertraline, which was increased up to 100 mg per day, along with Quetiapine reaching up to 150 mg per day. Apart from her mood improvement, she resumed her higher studies. No other suicidal crisis have appeared during the last one year and a half of follow up. Currently she is stable, with 100 mg of Sertraline and 50 mg of Quetiapine.

Images 1-2: Patient with full cutaneous sphacelous of the anterior face of the thorax, neck, face, almost complete of the abdomen.





Her diagnosis is major recurrent depression and traits of borderline personality. She has no physical TEN sequelae.

DISCUSSION

This is a TEN case with nearly 55 % of skin surface affected. The diagnosis was made on the 16th day after she started Lamotrigine intake –the usual range is between 7 to 21 days– although the first suspect symptoms happened a few days since she started using the drug. TEN is defined as acute skin failure, and it has as a prodrome a flu–type syndrome, with fever in almost 100% of cases, apart from odynophagia, rhinorrhoea and general discomfort: early detection of this prodrome, as this leads to early cease of the medication, is a measure that even though does not alter the general evolution it does decrease mortality[7]. Clinical Guidelines highly recommend to train patients for detecting these symptoms, apart from avoiding exposure to food or new make products, because of the allergenic risk involved in its use[1,2]. Likewise, the fact that the patient had chickenpox les than one month before, did not recommend use of Lamotrigine at that time[4].

The clinic picture of our case was a classic one, with spread purple/painful maculae, burning pain, posterior detachment of big flaps of skin, Nikolsky´s sign (when pressing blisters edges these spread, due to sphacelous of additional skin): the period of cutaneous sphacelous lasted one week. Likewise, affectation of oral/eye mucosas was present (as in 80 to 90% of all cases), although in this case there was no affectation of other areas (respiratory/digestive/genital mucosa). Recovery happened with no severe sequelae, and is worth to be mentioned, as there is no specific treatment proving such excellent response[4,5]. Lab data normality allowed us to discard other ADR as side effects of Lamotrigine, such as reactions of hypersensitivity with systemic symptoms and eosinophilia (DRESS syndrome[1]. In fact, there are no diagnosis tests for TEN/SJS, except skin biopsy and its relevant histological study reveal the typical pattern of cutaneous necrosis, lymphocyte infiltration and vacuolar basal changes[2,4].

A fact that influenced TEN occurrence in this case was dosage of Lamotrigine, which started with 50 mg and was increased –only after one week– up to 100 mg. There is a clear evidence that a high initial dosage and an increasing drug titration increases the risk of Severe ADR[14]. Current dosage titration, designed shortly after Lamotrigine was launched into the market, decreased incidence of severe rash from 1% to 0.1 – 001 % (without modifying 10% of frequency of benign eruptions in users)[14]. The standard compels to cease use of Lamotrigine before any rash, as it is not clinically possible to differentiate one with a benign evolution from another to end up in Severe ADR[5]. Although development of these ADR happens between 2 to 8 weeks after the drug is being used, we must be aware about the possibility of another further drug–drug interaction causing another rash (if Lamotrigine produces an eruption, there is a high possibility of a new outbreak when using another anticonvulsant, for instance)[4]. There is no difference regarding frequency of severe ADR among users of Lamotrigine suffering epilepsy/bipolar disorder diagnosis[7].

Even though our patient´s depressive episode showed some traits suggesting bipolarity (depressive episodes started before she was 25 years old, recurrence, irritable mood)[15], the need of a quick therapeutical response, and the low certainty of the diagnosis (validated instruments were not used for diagnosis of hypomania or bipolarity, for instance)[16], did not recommend Lamotrigine as a front line medication at that time. This Report is not aimed to review the patient´s diagnosis –in fact, the clinical information is not enough– but it is well known that Lamotrigine has a role in preventing depression relapse, but not in handling acute depressive episodes[17] –although currently that is to be reviewed–[15].

Likewise, there is evidence that Sertraline is associated to TEN development, although with a low risk[8]: this does not recommend choosing Lamotrigine in our case, if all the aforementioned is considered. If bipolarity diagnosis has some difficulties[18], in adolescents this is even more apparent: alleged hypomanias could be part of the common experience in adolescents[19] and in our case, even the presence of borderline personality traits (impulsivity, sudden mood changes) could have distorted the clinical picture[20]. Although there is no full agreement about

pertinence to prescribe antidepressants to patients with bipolar disorder –some people are in favor and other against it –[15], further evolution seemingly stable with Sertraline and low dosage Quetiapine, suggests this medicine would have been a better choice than Lamotrigine. Although this, of course, is not a therapeutical test that the final diagnosis is a possible bipolar disorder.

As a conclusion, Lamotrigine is a useful medicine as a psychopharmacological tool, as it causes less cognitive effects, less weight gain than other mood stabilizers, it is predominantly effective to avoid recurrence of depressive bipolar episodes[15,17]. Increase of its prescription in treatment of bipolar disorder, even in adolescents, demands recognizing the risks involving its use in order to minimize them, by means of a psycho education and a strict follow up. Psychiatric who prescribed this drug have been reported to have a lack of knowledge about the risks of Severe ADR which may cause the use of this medication and neglect of proper dosage titration[21]. The severity of potential consequences and the growing use of Lamotrigine impose a careful observance when selecting prescription of this medication.

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Correspondence to:
Lizardo Cruzado Díaz
National Institute of Mental Health “Honorio Delgado Hideyo Noguchi”.
Eloy Espinoza Street 709. Urb. Palao. San Martín de Porres. Lima 15102. Peru.
(051) 6149205
lizardo.cruzado.d@upch.pe