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ORIGINAL ARTICLE

DRESS syndrome after lamotrigine and valproic acid use in a bipolar patient: a case report

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Abstract
Background and objectives: Cutaneous adverse reactions are one of the commonest possible side effects of medication, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is one example. This potentially lethal syndrome usually presents with fever, rash and internal organ involvement which can begin sometime after the start of the offending drug. Its management commonly consists on the suspension of the offending agent and corticosteroid therapy. The authors present a clinical case of a DRESS reaction to mood stabilizers.
Methods: A case is described of a female patient with bipolar disorder type 1 who developed a DRESS Syndrome through valproic acid use, and which recovered after clinical management.
Results: This case represents the typical clinical case of a presentation of this rare syndrome which is usually linked to aromatic anticonvulsants use but more rarely may also appear with the use of non-aromatic anticonvulsants like valproic acid.
Conclusion: With this article the authors want to share a clinical case of this rare syndrome while highlighting the need for clinicians to be aware and alert the patients of this possible cutaneous adverse reaction to psychiatric drugs.

Introduction

Cutaneous drug eruptions are among the commonest adverse reactions occurring in hospitalized patients with its incidence ranging from 2 to 3%.[1–3] These reactions seem not to be dose related and generally reappear upon re-exposure to

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the same drug or other drugs of the same class. They include severe cutaneous adverse reactions, with increasing order of severity, as Erythema Multiforme (ER), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).[4–8] Mood stabilizers are related to the appearance of SJS and TEN which may constitute life-threatening conditions and may be related to the use of lamotrigine or valproic acid, among other mood stabilizers.[9–15] Additionally, a Drug Hypersensitivity Syndrome (DHS), sometimes also named as Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) may be related to these two drugs and while being more related to the class of aromatic anticonvulsants, usually linked to lamotrigine use, it has also been described more rarely with association to non-aromatic anticonvulsants like Valproic Acid.[16,17]

DRESS is a rare (frequency of 1/1000 to 1/10.000 exposures), yet potentially life-threatening reaction, presenting with fever, rash and internal organ involvement and which can begin in a short period of time, since the start of the suspected drug, that ranges between 1 and 12 weeks.[17] Several hypotheses exist relating to its pathogenesis with the one associating it to toxic metabolites being the most commonly accepted.[17] The management of this condition involves discontinuing the suspected drug while providing symptomatic support therapy.[17]

With this case report the authors want to share an illustrative clinical situation that shows this kind of rare adverse reaction, its management and evolution in a bipolar type 1 patient along with the problematic surrounding the difficulty for the future safe use of mood stabilizers on this patient.

Case presentation

Female patient, 44 years old, melanodermic, with a recent diagnosis of Bipolar Type 1 disorder. Admitted from the Emergency Department of our hospital with behavioral changes and insomnia which started a few weeks before and later evolved with an increase in severity. At admission she presented with a luxuriant look, showing hiperfamiliarity, elated mood, excessive talkativeness and racing thoughts while describing prodigality and paranoid ideation directed to her family without any insight for her clinical state which resulted in her involuntarily admission to the Psychiatric Department. From her clinical background there was a description of a previous cutaneous reaction to lamotrigine which resulted in a previous inpatient admission in Internal Medicine Department and a diagnosis of DRESS. After the present admission on psychiatric ward, the patient was prescribed with an antipsychotic (oral Aripiprazole 10 mg/day), a benzodiazepine (oral Alprazolam 2 mg/day), an antipsychotic for insomnia (oral immediate release Quetiapine 100 mg/day) and a mood stabilizer (Valproic Acid 1000 mg/day). On the 5th day of treatment she started a clinical picture consisting of cutaneous eruptions in her lower limbs which progressed to the face and trunk and occurring with fever and lower limb oedema. Analytically she presented with abnormal liver function (maximum values of: AST = 126UI/L, ALT = 268UI/L, alkaline fosfatase - 230UI/L), leukopenia ($3{,}2 \times 10\hat{9}$/L) and an increase in the C Reactive Protein (max of 90,6 mg/L). After this reaction, the mood stabilizer was rapidly suspended while keeping only the prescription of a tranquilizing benzodiazepine. Additionally, the antipsychotic was also suspended until later reintroduction. After being seen by Internal Medicine and Dermatology and diagnosed with DRESS she was prescribed with a systemic oral corticosteroid with Deflazacort 60 mg/day and Hydroxyzine 25 mg/day with a global positive progression of the clinical picture and later progressive suspension of these medications. After the normalization of the laboratorial parameters Aripiprazole 10 mg/day was first reintroduced, with a slow titration. Although lithium was considered as a possibility as a mood stabilizer the good evolution of the maniac symptomatology led to the decision of keeping the maintenance treatment restricted to the minimum with the patient being discharged only with the prescribed antipsychotic and follow-up Psychiatric, Internal Medicine and Dermatology appointments in outpatient setting. This clinical picture exposes a situation where after a previous cutaneous reaction to lamotrigine the patient developed the similar reaction to valproic acid. The potential cross-reactiveness between different mood stabilizers resulted in a restriction in the therapeutic available options and represents a significative therapeutic challenge on the future management of this patient.

Discussion and conclusions

This clinical case relates to a rare, yet possible, adverse reaction to mood stabilizers and which may potentially be life threatening and evolve negatively.[18] Nevertheless, on this situation and with the stopping of the offending agent and introduction of glucocorticoid therapy, the patient showed a significative and progressive improvement of the symptomatology and laboratorial abnormalities until their full normalization. Literature describes drug discontinuation as the main treatment with corticosteroids being secondarily used to suppress the systemic reaction although there isn't a full agreement on the medical management of DRESS.[19] Usually systemic corticosteroids are reserved for severe episodes of DRESS but due to the risk of relapse many clinicians prefer to use systemic corticosteroids even on milder forms of the syndrome.[19] As described in the literature there is an association of a first presentation of this kind with later similar presentations relating to cross-reactivity with other anticonvulsants.[20] In this situation there was an earlier cutaneous reaction to lamotrigine which occurred after weeks of its prescription and after reaching a 100 mg/day and which was described as presenting with malaise, fever, cutaneous rash, mucosal aftous lesions and laboratorial abnormalities (leukocytosis of $12.200 \times 10\hat{9}$/L with lymphocytosis of 68% and maximum increase in AST = 411 UI/L, ALT = 1316 UI/L, Alkaline Fosfatase = 326 UI/L, GGT of 650 UI/L and C reactive protein of 13.3 mg/L) with the treatment administered in this episode being systemic glucocorticoid – methylprednisolone – after the suspension of the suspected drug with subsequent improvement of the patient and which later repeated on exposure to valproic acid. The literature describes that this kind of reaction is even rarer than the reaction to lamotrigine as, usually, the main cause of this reaction are aromatic anticonvulsants.[21] On this clinical case the symptoms started in the commonly described time and presented with some of the usual key symptoms

(fever, malaise, skin eruption) described in DRESS.[17] As described in the literature the eruption affected the main areas involved in this kind of presentation (face, trunk and extremities) covering a significant body surface area and being associated to oedema.[17] Unfortunately, due to the patient in this case being melanodermic, it was not possible to document clearly the skin reaction with pictures. The involvement of at least one organ is quite common to this syndrome and affects approximately 90% of patients and, in this clinical case affected the liver.[18] Although there is a high variability in the presentation of this syndrome the presence of an exposure to a high-risk medication, rash eruption with progression to the commonly affected areas and being associated with oedema and systemic symptoms or organ involvement (fever, malaise, abnormal liver function tests) and laboratorial abnormalities consistently point to the presence of this syndrome. The fact that there was the absence of eosinophilia does not exclude this diagnosis as 10–50% of cases do not show it.[22] This case points to the importance of keeping an eye on possible adverse cutaneous reactions related to the use of commonly used mood stabilizers in order to rapidly discontinue the offending agent and start support treatment. Additionally, by presenting not only a reaction to lamotrigine but also a rarer subsequent reaction to valproic acid it adds to the rareness of this clinical case. Unfortunately, HLA genotyping which is described in literature with some alleles being linked to this clinical presentation was not possible due to this test being unavailable at the hospital. With this case report the authors want to present a rare adverse reaction to medication, which needs further etiological studies for a better comprehension of its basis, while highlighting the importance of a detailed previous clinical history, which should include earlier therapeutic adverse effects, in order to avoid the development of more severe clinical consequences when such an adverse reaction appears. Additionally, it is important to remain alert to the possibility of such a reaction while educating the patients to the key signals and symptoms related to it.

Ethical considerations

There was no use of human subjects in terms of experimentation on this article. All ethical procedures were performed including the assurance of privacy rights of the patient by omitting personal information that may lead to the identification of the specific patient.

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Conflict of interest

The authors have no conflict of interest to declare.

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