Letter to the editor

Mental disorder and mitochondrial dysfunction. Review on a case report

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Dear Editor,

Evidences support the existence of an association between mitochondrial dysfunction and psychiatric diseases, and mitochondrial abnormalities in many mental disorders (e.g., dementia, schizophrenia, bipolar disorder, autism, depression, obsessive-compulsive disorder, somatization disorder, eating disorders),[1] as well as the occurrence of psychiatric symptoms in subjects with primary mitochondrial diseases have been described.[2]

The aim of this article is to provide a literature review on the basis of the clinical case of a patient who, for years, was considered and treated as a mentally ill with a torpid and changing progression, and from this case reflect on how the psychic and organic spheres interrelate in the case of mitochondrial pathology, setting a clinical profile that must be taken into account.

Case Presentation

This was a woman with somatic symptoms of functional nature and non-identifiable physical correlation, who had been managed by the psychiatry department for years. The patient had been first diagnosed with a somatization disorder, and later on with a conversion disorder. Over time, the patient developed more severe symptoms, both psychical (affective psychosis) and somatic (unexplained fever and status epilepticus that resulted in patient admissions in the ICU and neurology department). This medical background guided the patient's diagnosis towards an "organic" disease. At present, an abnormality of the mitochondrial respiratory chain has been confirmed, and the patient suffers a severe physical and psychic impairment.

She had a normal development until the age of four, when she received antibiotic therapy for the treatment of a diarrheic process. After this episode, the patient developed deafness, which was attributed to an ototoxic effect of the drug she had received. Patient's persistent sensory deficiency determined the development of a "special" personality, and mistrust and suspicion marked her relationships from an early age. She completed normal primary school and, due to her sensory deficiency, she attended a specialized support center for a while. Afterwards, the patient completed a hairdressing professional training, and worked as a caregiver in a mentally handicapped support center. She married at the age of 25, and had her first and only child, a male, when she was 28 years old. The presence of an overprotective mother and a coldhearted and distant father should be emphasized in her family background.

A patient's brother has a neurosensory hearing loss, while a sister suffers "pseudo-migraine" and intolerance to exercise, and is currently undergoing neurology examinations. These data could be obtained after a thorough inquiry of the patient's family background, due to our suspicion of a mitochondrial origin of the disease, and had never been mentioned by the patient's relatives at the time of medical history obtaining.

The patient's psychiatric problems appeared at the age of 32 when, after 9 visits to the emergency department due to unspecific gastrointestinal symptoms (nausea, watery vomiting, and abdominal pain), the patient was referred to the gastrointestinal department. The organic origin of the clinical picture was ruled out after appropriate complementary examinations, and the patient's condition was deemed as functional. The patient was referred to the psychiatry clinics and, after a brief and fruitless time period, she was referred to the psychiatry outpatient care unit for an in-depth diagnostic assessment and intensified therapeutic approach, with a closer follow-up and psychotherapy initiation.

The psychopathological description obtained by the outpatient care unit resulted quite revealing of the patient's clinical profile: hypomimic face, bradykinesia, bradylalia and vague answers, scarce insight abilities, low mood with anhedonia, unplanned suicide ideation, and hypochondriac ideas with somatic anxiety. The personality profile showed a severe dependence on others, with neglected responsibilities, alexithymic traits, and difficulties for feeling verbalization. During her stay in the outpatient care unit, symptoms rated as "pseudo-neurologic" were evidenced, such as tremor in the right upper limb, and unsteady gait. Diagnoses of hypochondria and conversion disorder were proposed at discharge.

Three years later, the patient was admitted in the hospital's intensive care unit with unexplained fever, mutism, stiffness, diminished awareness level, and poor

response to antipyretic medication. She developed respiratory alkalosis, leukocytosis (13,000/mm^3), CPK 851 IU/L, and ketonuria. Initially, a possible malignant neuroleptic syndrome was suspected in relation to the low doses of risperidone that had been added to enhance patient's antidepressant therapy with duloxetine. The condition was benign and self-limited, and a final diagnosis of rhabdomyolysis with unspecified psychiatric disorder was made.

One year later, the patient's psychiatric condition complicated with maniac exaltation, congruent psychotic symptoms, severe behavioral disturbances (prodigality, pathologic gambling, alcohol abuse, lack of inhibition, money misappropriation, and childish and unorganized behavior), and self-care neglecting. The patient required hospital admission, and a maniac episode with psychotic symptoms was diagnosed.

Few months after this admission in the psychiatry ward, the patient developed fever and status epilepticus, and was admitted to the neurology department, where the possibility of an organic-based disorder was raised, this questioning the validity of the previous diagnosis of conversion disorder. Laboratory tests were conducted during this admission and showed high blood levels of lactic acid (28.5 mg/dl [normal range: 4.5-19.8 mg/dl]), and CPK (2715 IU/l [normal range: 10-120 IU/l). CT and MRI scanners did not reveal remarkable structural abnormalities.

The following diagnostic strategy was guided by the suspicion of a mitochondrial dysfunction (Table 1). Electromyogram results (vastus medialis, deltoid, and anterior tibialis) were normal. Trunk evoked potentials revealed a bilateral disturbance of nervous impulse transmission in the auditory pathway consistent with the hearing deficiency the patient had had since childhood (neurosensory deafness). The morphologic and histochemical features of a muscular biopsy did not show significant abnormalities. The examination of the enzymatic activity of the muscle mitochondrial respiratory chain revealed a 12.9 level of complex IV (cytochrome c oxidase) (Normal range: 30-73), this confirming the diagnosis of mitochondrial disease as a result of an isolated deficiency of complex IV. The deficiency was also evidenced in lymphocytes and fibroblast cultures. The study of the patient's mitochondrial genome did not reveal any pathological mutation, and a complete study of the nucleus exome is ongoing.

After diagnosis confirmation, our therapeutic strategy included a symptomatic treatment of neurologic, psychiatric, and gastrointestinal disturbances consisting of clonazepam 0.5 mg (1-0-1); levetiracetam 1500 mg (1-0-1); lormetazepam 1 mg (0-0-1); olanzapine 2.5 mg (0-0-1); and omeprazole 20 mg (1-0-0). In addition, replacement therapy with biotin, thiamin, vitamin C, and coenzyme Q10 was established. In spite of the therapy, the patient's outcome has been devastating. Cognitive and functional impairment are unstoppable, with subsequent exacerbations and predominance of somatic manifestations (fever of unspecified origin with affectation of the overall condition, level of awareness, and accumulative seizures) at present. The patient has shown increasing difficulties to care for herself, and needs assistance for toileting, eating, and dressing.

Table 1 **Diagnostic techniques for mitochondrial dysfunction**

Morphological and histoenzymatic studies: The existence of ragged red fibers (RRF) revealed by different staining techniques (trichrome Gomori or better succinate dehydrogenase (SDH) are indicative of abnormal mitochondrial proliferation, but their absence does not rule out mitochondrial disease (absent in some syndromes, such as Leber's optic atrophy, also according to the time course or the threshold effect) do not constitute in themselves pathognomonic signs (may be present in other myopathies). Often the RRF fibers are accompanied by COX negative fiber, however not all COX negative fibers are accompanied by RRF, suggesting that the enzymatic alteration is pre mitochondrial proliferation.

Electron microscopy. The most striking findings of structural changes in mitochondria are the increasing of number and size of mitochondria, anomalous peaks and paracrystalline inclusions. There can also be seen lipid or glycogen inclusions. Normality does not rule out cytopathy.

Biochemical study. Usually it carried out in homogenate muscle to evaluate the activity of the different complexes of the mitochondrial respiratory chain.

Genetic study (blood and muscle). Aimed to demonstrate alterations in DNA mt and DNA n. Cases of maternal transmission should be investigated to search for point mutations, DNA mt duplications / deletion. Sporadic cases may be related to simple mtDNA deletions.

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Discussion and Conclusion

There is increasing evidence that show the association between mitochondrial disorders and psychiatric disorders: alterations have been described in the number, form, function and localization of mitochondria in different psychiatric disorders, also changes have been found in the subunits of the chain respiratory, impaired defenses against oxidative stress, downregulation of mtDNA genes and brain metabolic dysfunction in mitochondria in various psychiatric disorders[2]. Therefore it have been considered the possibility that mitochondrial alterations might play a role in the pathophysiology of mental illness[2, 3-10].

The possibility of a mitochondrial disorder should be raised in the context of a particular constellation of findings, such as the presence of intermittent and progressive neurological and psychiatric symptoms, along with a family background of psychiatric disorders, mainly in case of maternal transmission.[11,12]

Different explanations have been proposed for the presence of psychiatric symptoms in mitochondrial disorders. In fact its high prevalence allows suspecting that could be a neurological manifestation of lack of energy in brain tissue because of the influence of epigenetic and environmental factors[13-15].

Somatoform disorders mimic a physical disease, and may cloud a diagnosis of mitochondrial disease[16]. In the case presented here, some symptoms were attributed to a conversion disorder (unsteady gait, tremor, deviation of the corner of the mouth, etc.), while other symptoms were associated to a somatization disorder (gastrointestinal symptoms) by the absence of an adequate medical explanation and the coexistence with clear psychological symptoms.

The intermittent and progressive appearance of neurologic and psychiatric symptoms, along with a family past history of psychiatric disorders, and the patient's worsening with the use of psychopharmacological therapy, should alert the psychiatrist on a potential mitochondrial disorder.

In the case presented here, the diagnosis of a respiratory chain deficiency provided consistency to the confusion of clinical manifestations. However, from a psychiatric point of view, the finding of an "organic" cause should not obviate that the patient suffers and interacts as a human being, with his/her abilities and limitations. It is imperative to offer a comprehensive care to these patients, including somatic as well as psychical aspects, and keeping in mind that, in many cases, the degenerative process will demand to meet the needs of both, the patient and his/her social and family environment.

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Cost-effectiveness analyses in neuropsychiatry and mental health

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Dear Editor,

Mental and neurological disorders pose significant loss of population health in terms of high morbidity and a large number of years lived with disability[1]. In order to prevent, treat and control global pandemic involving mental ill-health it is necessary to identify practices, interventions and programs that are effective (in terms of health gains) and efficient (at an economic cost that is affordable for health services and the society). Cost-effectiveness analysis[2] allows to evaluate the efficiency of programs and health interventions, facilitating the establishment of priorities in funding health technologies and services. Therefore, it is important to critically analyse information on methods and results of the cost-effectiveness analyses published in the literature, and establish their validity. Previous studies have systematically evaluated the scientific evidence on the presentation of the methodology and results of the cost-effectiveness using the quality-adjusted life years (QALY) gained as a measure of effectiveness[3,4]. However, so far it has not been described in sufficient detail the methodological characteristics of cost-effectiveness analysis evaluating interventions for mental and neurological diseases published in Spain[5,6].

In this letter, the methodological characteristics of the cost-effectiveness analyses of interventions aimed at addressing neurological and mental disorders (F01-F99, G06-G98 of the International Classification of Diseases, ICD-10 codes) are presented. To do this, we used the information from the cohort of cost-effectiveness analyses of healthcare interventions published in Spain during the period 1989-2014[4]. Briefly, we conducted a descriptive analysis of the methods and results of the 30 publications related to cost-effectiveness analysis of neuropsychiatric interventions carried out in Spain (until December 2014) presenting QALYs as a measure of health outcome.

Table 1 presents descriptive characteristics. Three (10.0%) studies indicated the existence of a research protocol. Most studies (24; 80.0%) used mathematical simulation models. Thirteen (43.3%) studies reported an adequate description of the characteristics of the population. Most interventions were classified as drug therapies (24; 80.0%) and two thirds (20; 66.7%) considered an active comparator as the alternative. Data on the effectiveness of interventions came from a single study in 9 (30.0%) analyses, and only 8 (26.7%) used estimates based on evidence synthesis (e.g., systematic reviews and meta-analysis of clinical trials). Less than half (12; 40.0%) of the studies reported a full description of the methods used to calculate QALYs. Most studies (17; 56.7%) reported that the evaluated intervention produced "more costs and QALYs" than the alternative or comparator.

In view of the results, we can say that there is significant room for improvement with regard to the presentation of important methodological aspects of published cost-effectiveness analysis. If the methods and results of the evaluations are not presented in a transparent and

Table 1 Descriptive characteristics of cost-effectiveness analyses of neuropsychiatric interventions in Spain (n=30)

Category	Characteristic	Number	%
Title	Identification		
	Specific terms "cost-effectiveness" or "cost-utility analysis" in title	27	90.0
Objective	Research question		
	Clear presentation of study question and its relevance for decision-making	25	83.3

Table 1 Continuation

Category	Characteristic	Number	%
Methods	Protocol		
	Existence of study protocol (or a priori established methods)	3	10.0
	Type of study		
	Model based	24	80.0
	Deterministic decision-tree model	6	20.0
	Markov model	12	40.0
	Other (or unclear)	6	20.0
	Non-model based	6	20.0
	Observational (non-interventional) study	3	10.0
	Randomized controlled trial	3	10.0
	Population		
	Number of participants included (or simulated)	18	60.0
	Adequate description of characteristics of the base case population	13	43.3
	Adults	13	43.3
	Type of interventions		
	Pharmaceuticals	24	80.0
	Device and procedures	5	16.7
	Educational/behavioural	1	3.3
	Type of comparators		
	Active alternative	20	66.7
	Usual care	7	23.3
	Placebo or do nothing	3	10.0
	Adequate description of interventions and comparators	28	93.3
	Study perspective clearly stated	28	93.3
	National Health System only	15	50.0
	National Health System and societal	7	23.3
	Societal only	5	16.7
	Hospital	1	3.3
	Time horizon reported		
	Short term	17	56.7
	Long term (>1 year)	13	43.3
	Diagram of model or patients/events pathway reported in a figure	23	76.7
	Assumptions discussed	23	76.7
	Model validation discussed (when applicable)	8	26.7
	Reasons for the specific model used (when applicable)	14	46.7
	Measurements of effectiveness		
	Based on a single study	9	30.0
	Based on evidence synthesis (e.g. systematic review and/or meta-analysis)	8	26.7
	Based on different studies without systematic evaluation	13	43.3
	Full description of QALY calculation	12	40.0
	Harms were considered	12	40.0

Table 1	Continuation		
Category	**Characteristic**	**Number**	**%**
Methods	Costs and resources information		
	Source of valuation for all cost items reported	30	100.0
	Quantity of resources	15	50.0
	Year of monetary units	28	93.3
	Costing		
	Direct costs only	30	100.0
	Direct and indirect costs	14	46.7
	Discount rate for costs and QALYs	11	36.7
Results	Net costs reported	25	83.3
	Net benefits reported	22	73.3
	Incremental cost-effectiveness ratio reported	26	86.7
	Confidence intervals (e.g. 95% CI)	7	23.3
	Cost-effectiveness plane	14	46.7
	Acceptability curves	14	46.7
	Sensitivity analysis reported	26	86.7
	For costs	25	83.3
	For estimates of effectiveness/efficacy	21	70.0
	For utilities	15	50.0
	For discount rates	5	16.7
	Type of sensitivity analysis		
	Deterministic univariate	12	40.0
	Probabilistic	14	46.7
	Results for the primary outcome in the base case scenario		
	More costs, more QALYs	17	56.7
	Less costs, more QALYs	9	30.0
	More costs, comparable QALYs	2	6.7
	Comparable costs, more QALYs	1	3.3
	Less costs, less QALYs	1	3.3
Discussion	Limitations of study discussed	28	93.3
	Results compared with those of other economic evaluations	20	66.7
	Hypothetical willingness-to-pay (WTP) threshold reported		
	<30,000 €/AVAC	1	3.3
	30,000 €/AVAC	20	66.7
	>30,000 €/AVAC - ≤50,000 €/AVAC	1	3.3
	>50,000 €/AVAC	3	10.0
	Unclear or not reported	5	16.7
	Study conclusions		
	Favourable	27	90.0
	Unfavouble	2	6.7
	Neutral	1	3.3

Tabla 1 Continuation

Category	Characteristic	Number	%
Other	Disclosed funding sources	28	93.3
	Private/for prodit	20	66.7
	Public	8	26.7
	None/not reported	2	6.7
	Disclosed conflicts of interest	18	60.0
	With conflicts of interest	15	0.50
	With no conflicts of interest	3	10.0
	Disclosed authors' contribution	7	23.3

QALY: Quality-Adjusted Life Years; 95% CI: 95% confidence interval

comprehensive way, it is difficult to establish the validity of studies which seriously hinders the transfer of knowledge to clinical practice. To help correct this problem and increase the scientific value of the cost-effectiveness analysis, it has been proposed the endorsement of reporting guidelines of research[7]. Reporting guidelines may be useful to researchers conducting studies and the reviewers and editors who evaluate them for publication because they help present a clear and coherent description of research. The incorporation of reporting guidelines in the peer review process could contribute to improve the quality of cost-effectiveness analysis that are published in journals, improving the transparency and credibility of future studies[8].

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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Lamotrigine induced dress syndrome in bipolar disorder

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Letter to the editor

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Dear Editor,

Lamotrigine use is officially approved in epilepsy and to prevent depressive episode in bipolar type I patients.[1] The drug is a voltage-dependent sodium channel inhibitor and it has been proposed as inhibitor of presynaptic glutamate release. Nevertheless, the specific mechanisms of action in bipolar depression still remain unclear.[2] Lamotrigine is widely used by psychiatrists in their clinical practice, thought it can cause frequently serious skin rash. It has been estimated that between 5 and 10% of patients who initiate lamotrigine treatment present a benign cutaneous reaction,[3] whereas around 0.3% could develop a severe skin rash with multi-organ dysfunction.[4] It is well known that an initial slow titration is crucial in order to minimize the risk of such severe events.[3] The Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare, potentially life-threatening adverse effect that can be induced by lamotrigine. It has been calculated that DRESS mortality is around 10%,[5] thus prevention and a rapid diagnostic are extremely important in order to immediately discontinue the responsible drug and to promptly establish corticosteroid treatment. Notwithstanding, the wide latency between drug exposition and syndrome occurrence, usually between 2 and 8 weeks, as well as the great variability in DRESS clinical manifestations, are factors that can increase the probability of diagnostic errors. Thus, the suspension of lamotrigine can be delayed which can lead to a worse clinical evolution and to a higher mortality risk. The purpose of this letter is to highlight the daily practice snares in achieving a correct diagnose of such diseases and underline the clinical relevance of misdiagnosis, considering the high associated mortality, through the description of a complex clinical case.

We report the case of a 25 years-old-man, diagnosed with Type-I Bipolar Disorder at the age of 19 in the context of a manic episode, who presented several manic and grave depressive episodes along the illness course. During the last hospitalization due to a manic episode with psychotic symptoms, lamotrigine was added to the routine treatment with lithium 1600 mg per day, risperidone 4.5 mg per day and lormetazepam 2 mg per day, in order to prevent eventual relapses in depressive episodes. When complete remission of manic symptoms was achieved, the patient was discharged after 17 days of hospitalization. Lamotrigine was initiated at 25 mg per day for 6 days, and the day of the discharge the dose was increased to 50 mg per day with apparent good tolerance. After 7 days with such dose, a titration to 200 mg per day in the next 16 days was recommended, because of the onset of depressive symptoms. After 35 days on lamotrigine treatment, an erythematous and pruritic rash appeared in his upper arms, for which the patient called on the emergency service. After physical examination, scabies infestation was diagnosed, and permethrin treatment was started as outpatient, without clinical improvement. Seventy-two hours later, in the wake of the skin rash dissemination, the patient returned to the emergency service. The physical examination evidenced erythroderma involving 70 to 80% of the body surface, secondary to the confluence of target lesions with central pustule, that was associated with severe facial edema and bilateral axillary and inguinal lymphadenopathy (Figure. 1A, 1B, 1C). No mucosal lesions were observed. The Nikolsky sign was negative. Furthermore, hemodynamic instability and fever at 39° C was detected, thus urgent hospitalization in Intensive Care Unit of internal medicine was carried out. The blood test showed leucocytosis with neutrophilia and eosinophilia, acute renal failure with severe hyponatremia, increase of hepatic enzymes and haemostatic disturbances (see Table 1 for details). After pharmacological anamnesis, DRESS diagnosis due to lamotrigine was made following RegiSCAR criteria[6] (Table 2). Besides the worsening of the clinical picture, lithium intoxication arose secondary to renal failure. Lamotrigine and lithium were stopped during hospitalization followed by fluid replacement therapy. Prednisone was administered at a dose of 1 mg per kilo per day, as well as intravenous antibiotics. Complete recovery was achieved after 2 months, without recurrences neither relapses of bipolar disorder. Lithium treatment was started over.

Discussion

The risk of severe and potentially lethal adverse events associated with lamotrigine, obliges to evaluate carefully the risk to benefit ratio for the patient. Moreover, as illustrated in the clinical case, the consideration of a wide number of factors is crucial in order to guarantee patients' safety. First of all, the lamotrigine titration faster than recommended by clinical guidelines can increase the risk of serious skin reactions[3] and induce the onset of a DRESS syndrome as in the exposed clinical case. It is fundamental to accomplish with the recommendations on the dosing, taking in account possible pharmacological interactions. Second, the time latency between lamotrigine introduction and the DRESS syndrome onset can also increase the risk of misdiagnosis. Patients must be informed about the risks of adverse dermatologic events associated with treatment, emphasizing the features of timing, thus in case of rash they can promptly come up to medical care. On the other side, physicians who evaluate dermatologic lesions should always carry out a pharmacological anamnesis, which considers at least a period of 3 months before the rash onset. Third, the high clinical variability of DRESS syndrome, which has an incidence between 1/1000 and 1/10.000[7] and a high

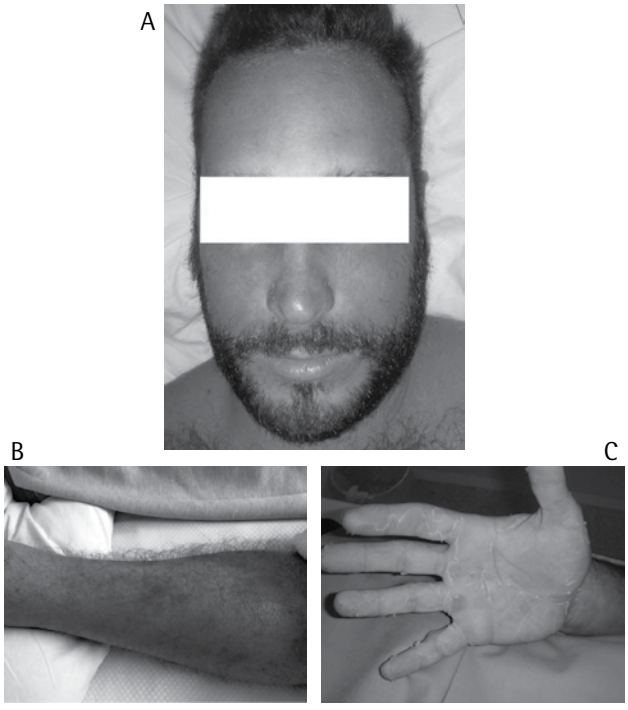

Figure 1 — *A. Erythroderma with facial edema. B. Confluence of target lesions, anterior side of left inferior member. C. Exfoliation of lesions, right hand palm*

mortality,[5] lies on the several patterns of skin eruptions that can induce to misdiagnosis, as in the case described. Indeed, the frequent reactivation of Herpes virus (HHV) 6, HHV 7 and Epstein-Barr virus observed in DRESS, can further contribute to the diversification of the dermatologic lesions. Moreover, the involvement of internal organs can also change. Beside liver and kidney, which are the more often affected organs,[8] it have been described cases of pancreatitis,[9] respiratory distress syndrome and myocarditis.[7] In such framework, the absence of a standard and certain diagnostic of the DRESS syndrome is not surprising. The criteria exposed in Table 2 permit an indicative probabilistic diagnosis. Thus, all this factors associated to DRESS syndrome, can lead to a delay in the correct diagnosis, deferring the therapeutic intervention, specially the discontinuation of the responsible drug, and increasing the mortality risk. Furthermore, in bipolar patients treated with lithium, the hemodynamic instability and the renal failure associated to the syndrome can bring to an elevation of lithium plasma levels, producing symptoms and signs of sever intoxication. Also, the DRESS syndrome treatment implies the use of high doses of corticosteroid,[10] with the consequent enhanced risk of a manic episode relapse.

Table 1 — **Demographic variables, vital signs and main laboratory results**

PATIENT CHARACTERISTICS	
Age (years)	25
Race	Caucasian
Educationlevel	High school education
Marital status	Single
Employment status	Partial time employed, University student
Allergies or treatment adverse effects	No reported allergies. Acute dystonia with risperidone
Substance use	Tobacco. Past cannabis and alcohol consumption
Diagnostics	Bippolar Type 1 Disorder
VITAL SIGNS	
Body Temperature	39.9 °C
Pulse rate	145 beats per minute
Respiration rate	25 breaths per minute
Blood presure	68/45 mmHg
MAIN LABORATORY RESULTS	
Leukocytes	$20.13x10^9$/L
Eosinophils	$3.8x10^9$/L
Neutrophils	$17.7x10^9$/L
Creatinine	2.18 mg/dL
Electrolytes (Sodium, Potassium)	123 mg/dL 4.8 mg/dL
Alanine Aminostransferase	115 UI/L
Hemostasis (PT, PTT)	17.5 sec - 34.7 sec
Arterial Gasometry (pH, pC02, pO2, HC03)	7.487 24.5 mmHg 111.5 mmHg 18.1 mmol/L
C-reactive protein	24.45 mg/dL
Lithemia	1.88 mEq/L
Hemoculture	Negative
Serology virus (HBV, HCV, EBV, HHV 6)	Negative

PT: Prothrombine Time; PTT: Partial Thromboplastine Time; pCO2: partial pressure of carbon dioxide; pO2: partial pressure of oxygen; HCO3: biarcbonate; HBV: Hepatits B Virus; HCV: Hepatitis C Virus; EBV: Epstein-Barr Virus; HHV: Herpes Human Virus

Table 2 RegiSCAR7 diagnostic score for DRESS diagnosis. In the patient a global score of 8 was calculated, making the DRESS diagnosis definite

Features	No	Yes	Unknown
Fever (>38.5 ºC)	-1	0	1
Enlarged lymph modes (> 2 sities, >1 cm)	0	1	0
Atypical lymphocytes	0	1	0
Eosinophilia	0		0
• 700-1,499 or 10%-19.9%		1	
• ≥1,500 or ≥20%		2	
Skin rash	0		0
• Extent >50%	0	1	0
• At least 2: edema, infiltration, purpura, scaling	-	1	0
• Biopsy suggesting DRESS		0	0
Internal Organ Involvemnt	0		0
• One		1	
• Two or more		2	
Resolution in more than 15 days	-1	0	-1
At least 3 biological inv done and negative to exclude alternative diagnosis	0	1	0

Final score: <2 = no; 2-3 = Possible; 4-5 = Probable; >5 = Definitive

In conclusion, in similar cases we should take into account the titration of lamotrigine, the severe symptoms onset delay, the polymorphism of cutaneous signs and the secondary complications due to metabolic changes induced by DRESS.

CONFLICT OF INTEREST

None.

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