Serotonin syndrome induced by a combination of venlafaxine and clomipramine. A case report

Francisco J. Pinel-Ríos[1]
Inmaculada Peñuelas-Calvo[2]
Nuria Cerezo-Ramírez[2]
Omar Hamad-Cueto[1]
Natalia García-Casares[3,4]

[1]Neurology Department, Hospital Clínico Virgen de la Victoria. Málaga, Spain

[2]Psychiatry Department, Hospital Clínico Universitario Virgen de la Victoria Málaga, Spain

[3]Medicine and Dermatology Department, Faculty of Medicine, University of Málaga, Spain

[4]Unit of Clinical Neurology, Center for Medical and Health Research, University of Málaga, Spain

Correspondence:
Natalia García-Casares
Departamento de Medicina y Dermatología
Facultad de Medicina
Boulevard Louis Pasteur, 32
29071 Málaga (Spain)
E-mail: nagcasares@gmail.com; nagcasares@uma.es

Dear Editor,

Although, since the 60's the processes involved in pharmacological overstimulation of serotonergic receptors were well known[1], the diagnostic criteria for Serotonergic syndrome (SS) was defined thirty years later by Sternbach[2]. SS is a serious and potentially life threatening condition which could manifest itself as a pharmacological side effect, clinically characterized by the presence of a triad of: mental abnormality, autonomic hyperactivity and motor hyperactivity. Drugs with serotonergic activity have a high potential to trigger it, especially when used in high doses or used concomitantly. It usually resolves within 24 hours of onset of symptoms, but in severe cases it can be prolonged and led to multiple organ failure and eventually death.

Many selective serotonin reuptake inhibitors (SSRIs) and dual antidepressants that increase the serotonin level in the brain have become the drug of choice for the pharmacological management of depression, generalized anxiety and neuropathic pain among others[3]. SS as an iatrogenic disorder is directly related to the use of these drugs, resulting from the interaction of two or more drugs used in combination including certain analgesics[4], antibiotics[5], antiretrovirals[6], antiparkinsonians[7], illicit substances such as lysergic acid (LSD) and 3-4 methylenedioxymethamphetamine (MDMA)[8,9].

Given the increased use of SSRIs, dual antidepressants along with other drugs in the general population, this syndrome is more likely to occur than before, so we should always be prepared to recognize it, make precise diagnosis and manage it with proper and prompt treatment. We present a patient affected by serotonergic syndrome due to a rare interaction of agents which is not described in the literature to date, followed by favorable resolution after the withdrawal of medication and supportive measures.

Clinical case

A 54 year old male came to the hospital with history of a moderate depressive episode (F32.1), and intense psychological comorbid anxiety associated with motor restlessness. Patient had no relevant medical history except hypertension controlled with enalapril 20mg daily. He was started on venlafaxine 150 mg/daily plus clorazepate dipotassium 10 mg/daily and levomepromazine 25 mg/daily with a sedative lormetazepam 1mg/daily for insomnia. The following month, due to worsening of his clinical symptoms intramuscular treatment with clomipramine was added (venlafaxine dose was not increased because of history of hypertension). After administration of the fourth dose of clomipramine, patient had an impaired level of consciousness, psychomotor restlessness, abnormal speech, disorganized behavior, myoclonus, anuria, constipation and autonomic dysregulation (tachycardia, sweating, etc.). He was immediately taken to the hospital emergency room.

On arrival the patient was afebrile, had a blood pressure of 140/90, heart rate was 113 bpm tachycardic and he had tachypnea at 23 breaths/min. Neurological examination revealed that the patient was somnolent, responding to commands and disoriented to time and place, and had no language deficit. The pupils were isochoric and normally reacting to light, cranial nerves were intact, Muscle tone, power, and sensations were normal. There were no signs of cerebellar dysfunction, parkinsonism or meningitis. However myoclonic jerks were visible in all four limbs with distal predominance. All deep tendon reflexes were present with clonus in left Achilles (detectable at 4-5 shakes) and plantar reflexes were flexor bilaterally.

The serum profile showed no abnormality and a normal coagulation. Biochemistry was unremarkable except elevated creatinine kinase to 54 UI/L. Cranial CT scan was performed and revealed no significant abnormality. Lumbar puncture was performed. Cerebrospinal fluid (CSF) analysis revealed no significant abnormality and xanthochromia, Gram stain of CSF was negative.

Due to the persistence of symptoms after 48 hours of observation, the patient was admitted to the neurological

unit for clinical stabilization. On admission repeat blood count, coagulation profile and biochemistry parameters (including CK) and urine analysis revealed no abnormality. Blood cultures revealed no growth. Repeat Lumbar puncture was performed. CSF serology and culture were negative. Onconeuronal antibodies were also absent in serum and CSF.

All medications were stopped except supportive measures including treatment of hypertension with enalapril and myoclonus with clonazepam 0.5 mg/12 hours. During the next 48 hours, the patient had a favorable resolution of his organic symptoms.

Following which the patient was shifted to psychiatric care. After ruling out all the possible causes of the patient presentation we finally arrived to the diagnosis of Serotonergic syndrome caused by interaction of venlafaxine and clomipramine.

Discussion

The patient had serotonergic syndrome due to an interaction between venlafaxine and clomipramine which was not previously described in any literature, though serotonergic syndrome because of interactions between other drugs have been reported in the past[7-10]. Both venlafaxine and clomipramine exert their antidepressant effects by inhibiting both serotonin and noradrenaline reuptake through its metabolites (o-desmethylvenlafaxine and desmeticlomipramine respectively). The SS is secondary to excessive stimulation of postsynaptic serotonin 5-HT1A and 5-HT2A receptors at central and peripheral level[2,3]. One should suspect serotonergic syndrome when patient presents with characteristic signs and symptoms in presence of use of one or more serotonergic agents simultaneously and after exclusion of other diseases[11]. Table 1 shows the drugs that are most often associated

Table 1 Mechanisms of serotonin syndrome and related drugs

Increased synthesis serotonin	Inhibition metabolism serotonin	Increased secretion serotonin	Stimulation receptors postsynaptic	SSRIs and some related drugs
L-tryptophan	*MAOI*	Amphetamines	Buspirone	*SSRI*
	Tranylcypromine	Mirtazapine	Lithium	Citalopram
	Phenelzine			Fluvoxamine
	MAO-A inhibitor			Fluoxetine
	Moclobemide			Paroxetine
	MAO-B inhibitor			Sertraline
	Selegiline			Venlafaxine at low doses
				Tramadol
				Trazodone
				Sibutramine
				Tricyclic antidepressants
				Amitriptyline
				Clomipramine
				Doxepin
				Imipramine

SSRI: selective inhibitors of serotonin reuptake; MAO: monoamine oxidase inhibitor, MAO-A: monoamine oxidase type A, MAO-B: MAO type B

with the syndrome[10]. In most cases (85%) is due to the drug interaction of two or more drugs when used in therapeutic doses and less frequently (15%) as a result of a single drug overdose[12].

The SS is characterized by a clinical triad of mental abnormality, autonomic hyperactivity and motor hyperactivity.

Autonomic hyperactivity is the most common manifestation of SS. Diaphoresis and hyperthermia occur in about half of the patients (45%). Hypertension (35%) is more frequent that hypotension, the latter being associated with a poorer prognosis. Other symptoms include tachycardia (36%), mydriasis (28%), tachypnea (26%) and nausea (23%)[12,15].

The most common manifestations of motor hyperactivity are myoclonus (58%), hyperreflexia (52%) and muscle stiffness, especially in the lower limbs[12,15].

Restlessness (48%), tremor (43%), ataxia (43%), hyperactivity (18%) and seizures (14%) can also occur[12].

The cognitive and behavioral manifestations are present in about half of the patients and manifest as confusion (51%), disorientation (51%), irritability (34%) and agitation (34%)[12,15].

Although no specific laboratory findings have been described, yet there can be slight elevation of the CK level and WBC count[16,17].

The diagnosis of SS is based on the presence of four major symptoms or three major and two minor, according to the criteria proposed by Sternbach, which was subsequently reviewed by Radomski et al.[18] (Table 2).

Table 2 Serotonin syndrome diagnostic criteria*

Functional impairment	Major symptoms	Minor symptoms
Mental or behavioral	Confusion/comma	Anxiety
		Agitation
		Fatigue
		Insomnia
Autonomic	Fever/ hyperthermia	Tachycardia/tachypnea
	Diaphoresis	Hypotension/ hypertension
		Dyspnoea
		Redness
		Diarrhea
Neuromuscular	Clonus[1]	Incoordination
	Hypertonia[1]	Mydriasis
	Myoclonus[2]	Akathisia
	Tremor	Ataxia
	Hyperreflexia	

*Must meet four major symptoms or three major and two minor
[1]Clonus and hypertonia are more pronounced in the lower limbs.
[2]Patients may experience a mild form of excessive serotonergic stimulation, which can manifest as mild tremor, myoclonus, anxiety and restlessness that lasts for weeks or months.

The differential diagnosis of SS must be made with entities capable of producing autonomic dysfunction, encephalopathy and neuromuscular involvement including neuroleptic malignant syndrome, heat stroke, delirium tremens, intoxication or withdrawal of sympathomimetic agents (cocaine, amphetamines, NMDA, LSD), malignant hyperthermia, sedative-hypnotic withdrawal, carbamazepine or lithium toxicity, poisoning by drugs with adrenergic or anticholinergic activity, metabolic encephalopathies, limbic encephalitis by neuronal antibodies against surface antigens (NMDAR, anti-AMPAR and anti-GABAR) and by paraneoplastic syndromes and herpes encephalitis among other infections.

The five pillars in the treatment of SS are: a) The cessation of all serotonergic agents, b) Normalization of vital signs, c) Sedation with benzodiazepines, d) The administration of serotonergic antagonists, e) Assessing the need to resume the use of serotonergic agents after resolution of symptoms[19].

In most cases, the discontinuation of medications causing the SS, and supportive measures of sedation with benzodiazepines are sufficient, with resolution within 24 hours. Moderate cases require more aggressive treatment of the autonomic instability and possible treatment with a serotonergic antagonist. In severe cases, with hyperthermia higher than 41.1°C, sedation and mechanic ventilation could be necessary[19].

The SS is an entity often underdiagnosed, but it is essential to have it in mind, because it is potentially lethal if prompt diagnosis is not made and appropriate treatment is not given.

SS should be considered as the differential diagnosis of patients with similar clinical picture and treated with

serotonergic agents. One should always bear in mind the possibility of SS due to its increasingly common occurrence in any emergency hospital setting.

CONFLICT OF INTERESTS

No conflicts of interest or funding sources.

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Serotonin syndrome, rhabdomyolysis and convulsion associated with drug interaction between venlafaxine and amoxicillin/clavulanic acid

Anxo Fernández-Ferreiro[1,3]
Antonio Pose-Reino[2]
Francisco Martinez-Bahamonde[1]
Marion Paris[4], Emilie Guemas[4]
Miguel González-Barcia[1,3], MJ Lamas[1, 3]

[1]Servicio de Farmacia, Xerencia Xestión Integrada Santiago de Compostela (SERGAS)
[2]Unidade Pluripatoloxía e Idade Avanzada, Medicina Interna, Xerencia Xestión Integrada Santiago de Compostela (SERGAS)
[3]Grupo Farmacología Clínica. Instituto de Investigación Sanitaria, Santiago de Compostela (IDIS-ISCIII)
[4]UFR Sciences Pharmaceutiques et Ingiénerie de la Santé, Université d'Angers

Correspondence:
Anxo Fernández Ferreiro
F.E.A. Farmacia Hospitalaria
Servicio de Farmacia
Xerencia Xestión Integrada Santiago de Compostela
Calle A Choupana s/n
15706 Santiago de Compostela (Spain)
Tel.: +34981955160
E-mail: anxordes@gmail.com

Dear Editor,

Drug interactions continue to gain prominence in the daily clinical practice due to polypharmacy[1] of an aged population requiring more psychopharmacological treatment[2].

Amoxicillin is a beta-lactam antibiotic usually associated with the clavulanic acid for the treatment of several infections[3]. However it has an immunomodulatory effect on

the neurotransmitters that is hardly known. Therefore it may carry important clinical implications specially for patients treated with antidepressants[4,5].

We face the case of a patient admitted in the internal medicine unit with a clinical picture of rhabdomyolysis, hyponatraemia and convulsions. It was probably caused by a serotonin syndrome triggered by a drug interaction between venlafaxine and amoxicillin/clavulanic acid.

Clinical Case

It is a caucasian woman of 66 years. She has history of obesity, hypertension, diabetes, MALT lymphoma, intestinal metaplasia, fibromyalgia, arthrosis, subclinical hypothyroidism, dysthymia and histrionic personality disorder. We check the patient receives her home treatment under family supervision. It contains psychotropics (venlafaxine 150 mg/24h, mirtazapine 30 mg/24h, clonazepam 9 drops/24h, quetiapine 50 mg/8h, clorazepate 50 mg/8h and lormetazepam 2 mg/24h), irbesartan 300 mg/24h, simvastatin 10 mg/24h and lansoprazole 30 mg/24h. The patient comes to the emergency unit and is admitted due to disorientation, lack of connection with the environment, enervation, lifeless gaze, inability to speak, reduction in the diuresis and excessive sweating. Interesting analytical and clinical data are: a moderate-severe (125 mmol/L) case of hyponatraemia stands out, rhabdomyolysis (pain, muscle weakness, convulsions and CPK>7000.0 UI/L), renal insufficiency (blood creatinine = 1.49 mg/dl). The Patient is on complete fasting without oral medication, the hyponatraemia is treated with isotonic fluid therapy and the convulsions with levetiracetam. The patient experiments a good clinical course and evolution with normal values of natremia and progressive decrease in the values of CPK. This clinical picture raises suspicions of a severe case of rhabdomyolysis with deterioration of the consciousness as first working diagnosis. It also shows traits suggesting the classic triad of the serotonin syndrome caused by the combination of venlafaxine and mirtazapine. These drugs increase the serotoninergic neurotransmission activity[6].

After consulting the pharmacy department about the possible cause, it is recommended to consider other medical options because the home treatment had not changed during the last year. On the other hand the clinical picture is not connected to the recent introduction of these drugs. Therefore the patient is asked about the intake of any other medication out of her chronic treatment. She replied she had been to the dental practitioner for a tooth extraction before the admission. The practitioner had prescribed her antibiotherapy consisting of amoxicillin/clavulanic acid 875/125 mg after the intervention.

Afterwards, the potential drug interactions of her home treatment are analysed using the databases Micromedex® and Drug-interactions®. Several major drug interactions are found in her chronic home treatment which might cause grave adverse reactions such as: torsade de points (quetiapine/venlafaxine), grave CNS-depression (mirtazapine/benzodiazepine) or serotonin syndrome (venalfaxine/mirtazapine)[7]. We would like to emphasise the risk of serotonin syndrome also caused by the interaction between venlafaxine and amoxicillin/clavulanic acid. This is very probable because of the period of time between the prescription and the appearance of the clinical picture. This drug interaction has been described by other authors before but no tool has been used to demonstrate the causality, nor an explanation of the pharmacodynamics and pharmacokinetic mechanisms causing the interaction.

Discussion

In order to evaluate the causality of the adverse effects due to the drug interaction, we need a careful evaluation of the attributes of the precipitating drug and of the object drug. The Naranjo nomogram and Karch-Lasagna's have been designed to evaluate adverse effects related to the use of a specific drug and not as a part of a drug interaction[9,10]. However, the drug interaction probability scale (DIPS) developed by Horn in 2007 was specifically designed for the presence of two or more drugs[11].

The table 1 shows the items from the DIPS next to the specific answers for this particular case in order to obtain the probability of cause of the described clinical picture with the drug interaction. Supporting decisions based on evidence about drug interactions requires the coherent application of clear systems to assess the evidence[12]. In this case, the DIPS scale is used to inform of the possible causality between the described clinical picture and the interaction between amoxicillin/clavulanic acid and venlafaxine. Mirtazapine is a central presynaptic alpha-2 antagonist which increases central noradrenergic and serotonergic neurotransmission while venlafaxine is a serotonin and noradrenaline reuptake inhibitor and both are used as antidepressants[13]. However, amoxicillin's and clavulanic acid's immunomodulatory mechanism in the brain is only described in studies performed in vitro and it is not been used in the clinical practice with that objective. Several authors mention the dual antidepressant effect of clavulanic acid based on serotonin and dopamine reuptake inhibition. This is possible due to the rise in the translocation of Munc18-1 and Rab4 from cytoplasm to plasma membrane increasing the release of neurotransmitters from vesicles to the synaptic cleft[14].

Today, there are several drugs available in the market used to treat anxiety and depression such as monoamine-ox-

Table 1 Use of Horn nomogram for the drug interaction between amoxicillin-clavulanic acid and venlafaxine and its connection to the development of serotonin syndrome

1. Are there previous reports of this interaction in human beings?	Yes (+1)	There are several previous studies where serotonin syndrome was caused by the interaction of amoxicillin and venalfaxine.
2. Is the observed interaction consistent with known pharmacological properties of the drug precipitating drug?	Yes (+1)	Despite previous studies have identified the drug interaction in humans, the possible mechanism causing it has not been found. New papers suggest an immunomodulatory effect of the beta-lactam ring and beta-lactamase inhibitor.
3. Is the observed interaction consistent with known pharmacological properties of the object drug?	Yes (+1)	Serotonin syndrome associated with venlafaxine is widely described in scientific literature specially when the treatment also consists of other serotonergic drugs such as mirtazapine.
4. Does the adverse reaction occur after a reasonable period of time after the intake of the drug which triggers the reaction?	Yes (+1)	The patient underwent her home treatment and the symptoms causing her admission in the hospital appeared two days after starting the treatment with amoxicillin/clavulanic acid.
5. Has any alteration been observed after a change in the treatment including the drug which triggered the interaction and the adverse reaction?	Yes (+1)	Once amocillicin-clavulanic acid and the rest of drugs were eliminated, the adverse effects disappeared.
6. Does the interaction reappear when the precipitating drug is reintroduced?	NA (0)	The drug has not been reintroduced. The antibiotic prophylaxis was interrupted after the dental intervention due to the favorable progress.
7. Are there any other reasonable alternative causes of the event?	No (+1)	Other causes of the symptoms might have existed, they can be connected with the basic treatment but it is not reasonable to think so because this is chronic medication which hasn't been changed. Quetiapine and simvastatin could cause rhabdomyolysis and mirtazapine and venlafaxine's natural serotonergic power could cause the mentioned clinical picture.
8. Has the drug involved in the event been found in blood or other fluids in concentrations consistent with the proposed interaction?	NA (0)	Tests showing the blood levels of involved drugs are not performed in the clinical practice.
9. Has the interaction been confirmed by an objective test?	Yes (+1)	The clinical picture observed in the patient and the analytical findings are indicative. Dysautonomia (intense sweating), neuromuscular disease (high CPK),renal insufficiency (increase of blood creatinine in relation to baseline creatinine).
10. Has the interaction been more intense when the dose of the precipitating drug has been increased or less intense when the dose of the precipitating drug was reduced?	NA (0)	Drugs presumably involved in the adverse reaction have not been administered again.
Score and result of causality	7	Probable

idase inhibitor, antidepressants, benzodiazepines or selective serotonin reuptake inhibitors (SSRIs). Specific signalling pathways are affected by each one of these drugs except for clavulanic acid. Therefore it may be considered as a pharmacotherapeutic alternative for patients suffering from depression. While this therapeutical strategy is not developed, the current approach should be focused on handling with caution the concomitant prescription of amoxicillin/clavulanic acid for patients being treated with psychoactive drugs interfering with the serotonergic transmission. We do not know if the association of amoxicillin/clavulanic acid with a hypothetical prescription of venlafaxine in monotherapy could have caused the mentioned clinical picture. Therefore more studies are necessary to find the real casuistry of this drug interaction and we must increase reports on adverse drug reactions.(www.notificaram.es). Finally, we should not dismiss other pharmacogenetic implications that might be involved in certain individuals' tendency to suffer adverse

reactions[15]. Increasing the investigation http://www.notificaram.es in this field is essential to allow optimisation and personalisation of pharmacotherapy.

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Diaphragmatic flutter as conversion symptom: a case report of a neurology-psychiatry-interface disorder

Giovanni Oriolo[1]
Alejandro Quílez[2]
Luis Pintor[3]

[1]Departamento de Psiquiatría y Psicología, Instituto Clínico de Neurosciencias Hospital Clinic de Barcelona, Spain

[2]MD, Neurologo, Departamento de Neurología, Hospital Universitari Arnau de Vilanova, Lleida, Spain

[3]MD, Psiquiatra, PhD, Unidad de Psiquiatría de Enlace y Psicosomática, Departamento de Psiquiatría y Psicología, ICN, Hospital Clínic de Barcelona, Spain

Correspondence:
Giovanni Oriolo
Departamento de Psiquiatría y Psicología,
Instituto Clínico de Neurosciencias
Hospital Clinic de Barcelona
C/Villarroel 170
08032 Barcelona, Spain
Tel.: (+34) 93 227 5400 int.2323
E-mail: oriolo@clinic.ub.es

Dear Editor,

Diaphragmatic flutter (DF) is a rare form of segmental myoclonus characterized by a sudden involuntary, repetitive and rhythmical contraction of the diaphragm and/or other respiratory muscles.[1] No consensual diagnostic criteria exist for DF. Clinical symptoms, electromyographies (EMG) and video-electroencephalogram (video-EEG) can help to confirm its diagnosis.[2] Conversion disorder (CD) is one of the possible causes of diaphragmatic flutter,[3] as well as encephalitis, epilepsy and spinal cord trauma.[1] Many physicians still regard such disorders as a failure to detect the real cause of the symptons or a failure to highlight a measureable alteration in these.[4] In the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders an effort was made towards a better recognition of the complexity of the interface between psychiatry and medicine. The official term "Functional neurological symptom disorder" was added next to the more classical term "Conversion disorder" to refer to an

abnormal functioning of the central nervous system. This distinctive diagnostic feature was based on the recognition of positive symptoms and signs together with affective, cognitive and behavioral components. These changes aim was to increase reliability and reduce the pejorative and demeaning concept of "unreal" symptoms. Nevertheless, many patients still fall in between the fields of psychiatry and neurology, leading to mistreatment and abandonment and at the same time adding to the existing conceptual and terminological confusion.[5] Therefore, the purpose of this case report is to highlight how the epistemological mind-body dichotomy still dominates medical approaches, with often serious and tragic consequences in the patient clinical evolution.

We present the case of a 52-year-old woman diagnosed with DF at the age of 38 due to crisis of inspiratory and espiratory dyspnea and abnormal abdominal movements. At the disease onset, different triggers were identified (familiar discussions, pressure in work environment), but they desappeared during the illness evolution. Due to the severity and frequency of the crisis and the many hospitalizations in critical care units, a tracheostomy was implemented to assure appropriate ventilation during the crisis. During the follow-up, multiple exams were carried out in order to confirm the DF diagnosis and to find a possible etiology. A simple spirometry shows a mild restrictive pattern, while a basal EEG (Figure 1) and a Video-EEG were done to discard epileptic activity. A diaphragm electrophysiological study was carried out on three separate occasions. Only in one study was the presence of "irregular, spontaneous and high-frequency motor unit discharge" documented, whereas in the other two studies no spontaneous activity was recorded. Different pharmacological strategies were tested for 15 years with bad results. A partial response, consisting in reducing the frequency of episodes and a better symptomatic control of each crisis, was observed with 100 mg of midazolam in pump infusion and 15 mg subcutaneous as rescue during each crisis.

At the age of 47 the patient was in a traffic accident and developed lower extremity paraplegia with tactile, thermal and pain hypoesthesia. Nevertheless, excepting the evidence of systematic incongruencies during different neurological exams, no structural disease was found or observed in the spinal cord magnetic resonance (Figure 2). In spite of rehabilitation treatments, no improvement was observed and the patient still depends on a wheelchair as her means of mobility. During this period, a psychiatric follow-up as an outpatient was begun. Two past traumatic events were underlined in the patient's biography: the father's death when she was 13, and a troubled and painful childbirth, so much that a laparotomy was made. The psychopathology evaluation stood out hypothimia and apathy, even if the affect was reactive and little congruent

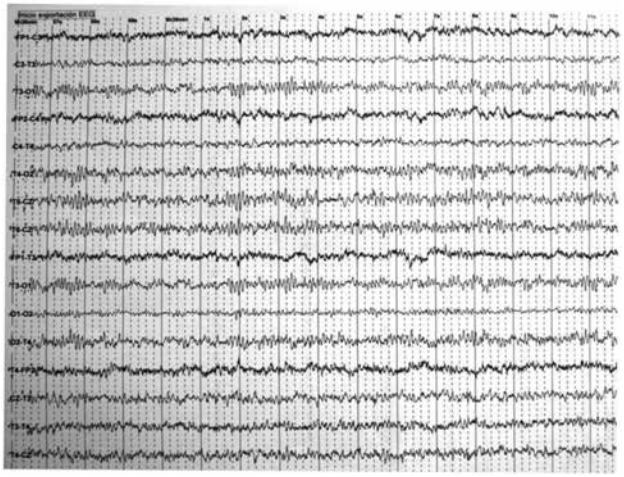

Figure 1 — *Basal Electroencephalography (EEG). The physiological brain activity registered by the means of basal EEG rules out epileptic etiology of the diaphragmatic flutter*

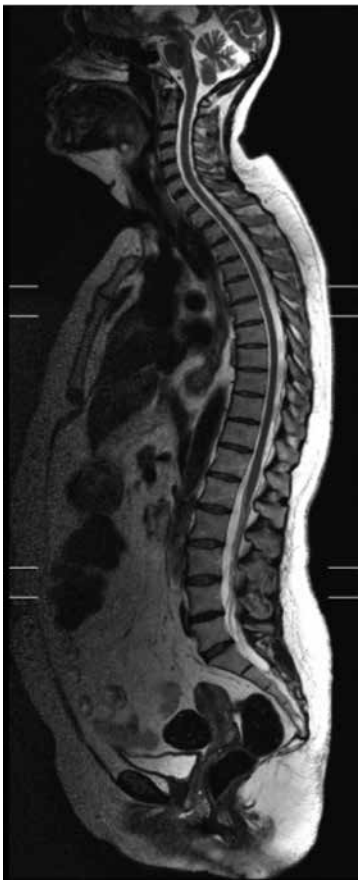

Figure 2 — *Sagittal T2 weighted vertebral magnetic resonance. No medullary lesions were observed*

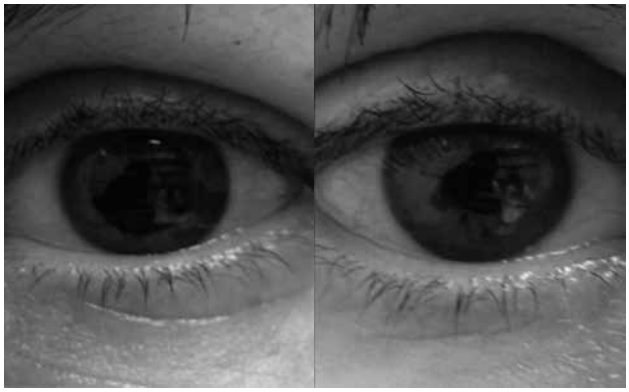

Figure 3 | *Left eye non-reactive mydriasis due to local iris dysfunction*

to thoughts content, without clincal relevant anxiety. As years go by, the ideo-affective incongruence was more apparent, and the concept of *belle indifference* was used to describe it in some circumstances.

This clinical picture became more complicated because of incapacitating urinary incontinence, which in turn led the patient to a domestic intermittent auto-catheterization. By means of a urinary tract dynamic study, it was possible to diagnose a dysfunction of urinary bladder control. Furthermore, that same year the patient suffered transient blindness in her left eye and a non-reactive mydriasis due to iris dysfunction remained as a consequence (Figure 3). No vascular neither ophtalmological causes were found.

Discussion

Considering the DSM-5 criteria, a diagnosis of CD would appear to be clear. Paraplegia, bladder control dysfunction and transient blindness cannot be explained on the basis of any structural neurological lesions. Nevertheless, DF clinical features, the presence of spontaneous diaphragmatic activity registered in an EMG and the absence of any clear DF diagnostic criteria, make the CD diagnosis more controversial. The DF transitory resolution by the means of frenic nerve blockade with methilprednisolone infiltration at C4 root level, would have helped to orient an inflammatory cause. However, high dose corticosteroid treatment was made for a long period, without any benefit.

It is known that psychological aspects are critical not only in the development, expression and deterioration of functional symptoms, but also in the manifestation of physiological activities, such as breathing. Emotional reactions such as anxiety or cognitive functions such as speaking can influence the pattern and depth of breathing.[6] As reported by Kobayashi et al.[7], these pathways might play a significant role in the development of DF. In our case, crisis were often triggered by stressors or intense emotional situations, and accompanied by a persistent and life-threatening acute respiratory insufficiency. When describing DF, some authors highlight the neurological origin of the disease, basing themselves either on the demonstration of diaphragmatic spontaneous and involuntary activity,[8] or on the presence of a dual respiratory rhythm, a voluntary breath superimposed to the pathological involuntary one.[2,9] On the other hand, other authors[3] point out the importance of voluntary control in the development of DF, even maintained that a patient could consciously provoke a DF. Moreover, the same changes mentioned before in mental activity can influence other motor or sensory voluntary functions, such as motion, emiction or vision, via the same pathways. All this raises the question: wherein does the pathology really lie? We believe that the conversion *vs* neurological disease dichotomy is insufficient to explain our patient's reality, in the same way that the separation between the voluntary and the involuntary of the neurological functions can be a wrong approach. An alteration of the psychophisiological homeostasis (a "psychosomatic status") may probably be crucial in the appearance of a disorder in the behavioral control of breathing, motion, emiction and vision, but is not comprehensive enough to describe the complicated medical condition of our case. In an attempt to go beyond Cartesian dualism, the concept of a Neurology-Psychiatry Interface Disorder, introduced by Strassnig et al.[10], may better describe our patient's disease and propel the development of new therapeutic strategies.

CONFLICTS O INTEREST

The authors declare no conflict of interest.

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