Letter to the editor

Cotard's Syndrome in a patient with Major Depressive Disorder: Case Report

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Dear Editor,

Cotard's syndrome is a rare psychiatric condition, first described in 1880 by Jules Cotard, whose central symptom is delusions of negation and which, in its entire form, the patient deny the existence of parts of their bodies or even their whole bodies, leading to denial of the world around them[1]. Ramirez-Bermudez et al.[2] reported that of 479 Mexican patients with a primary psychiatric disorder, including 150 patients with schizophrenia, three had Cotard's syndrome (0.62%), all of them with psychotic depression. In 2013, Stompe and Schanda[3] reviewed 346 cases of schizophrenia and found three patients with Cotard's syndrome (0.87%).

Due to the rarity of this clinical presentation, we consider relevant to present the case of a patient with major depressive disorder who developed this syndrome. It should also serve to draw attention to an adequate, not a reductionist, psychopathological examination.

Case report

It is about a 71-year-old male patient. His family psychiatric background included a son with paranoid schizophrenia and a daughter with recurrent depressive disorder. He does not have a personal somatic or psychiatric background. The functioning level of the patient before the disease was appropriate in relation to her cultural beliefs, showing good work performance.

Three months before the admision to our Service, the patient was informed about a legal problem against him, from that moment he began to have sad and anxious mood, daily crying to night dominance, anhedonia, persecutory ideas (he thought the police were searching him), as well as ideas of guilt, insomnia of conciliation, hyporexia, marked social withdrawal and various "strange" sensations, both his own and the external world, which the patient could not explain.

As the days passed, the symptoms described above were getting worse. One month before admission, the patient makes a suicidal attempt; so he is taken to the emergency service of a hospital in Lima. The patient reported that he did not tolerate anxiety and fear with guilty feelings, so he decided to put an end to his life. He was discharged the next day, after the evaluation by a psychiatrist. Later, he frequently went to an outpatient psychiatric clinic, where psychopharmacological treatment began. Family members do not remember the name or dose of the medications.

After 15 days of treatment there was no evidence of improvement. Added to the aforementioned symptoms were verbal auditory hallucinations that command the patient to end his life ("kill yourself", "throw yourself from the second floor"), besides insult him ("you are a sinner"). All of this hallucinations generated too much anxiety and fear. Later the relatives noticed some bizarre behavior; the patient left his house at dawn, remaining immobile in the middle of the highway for several minutes, putting his physical integrity at risk. Due to all this, the relatives of the patient decide to take it to the emergency department of our hospital.

Being hospitalized, he told us that he was "dead" and "rotten on the inside", "he had no spirit", additionally he said he was "guilty of great world catastrophes, tsunamis, hurricanes, etc". He found himself "condemned" so that "God never again gave a spirit" and "ended eternally in hell".

The physical examination was not contributory to some somatic pathology. On mental examination we find an awake patient, oriented in person, partially oriented in time and space, with depersonalization and derealization, imperative auditory hallucinations, delusive ideas of persecution, denial, condemnation and immortality, increased question-answer latency, bradypsychic thinking, structured autolytic ideas, depressive mood, paranoid anxiety, feelings of guilt, anhedonia, social withdrawal, hyporexia, global insomnia, some psychomotor restlessness. Severe cognitive impairment was evidenced in the Screen for Cognitive Impairment in Psychiatry (SCIP).

In blood analysis (blood count, vitamin B12, folic acid, liver profile, coagulation profile, glucose, urea and creatinine) no alterations were found. On brain computerized tomopraphy (CT) scan no alterations were found.

He was diagnosed with a major depressive disorder with psychotic symptoms (296.23). The treatment consisted of fluoxetine 40 mg/day and olanzapine 20 mg/day, which showed a significant improvement at three weeks of treatment. Delusive ideas were no longer maintained and affective symptomatology improved. This observation was shared by the relatives, who reported seeing him much better, so he was discharged. Currently the patient presents a persistent emotional disturbance of depressive type.

Discussion

The conceptual evolution of Cotard's syndrome has gone through several vicissitudes throughout its history. Did Cotard try to describe a new disorder or rather a severe form of melancholia? This question was discussed intensively from the beginning of the description made by Cotard and still remains unanswered[4]. Throughout the 20th century Cotard's syndrome suffered, along with other clinical phenomena, a semantic degradation, this partly due to the use of operational definitions, which gradually converted the psychopathology into lists of criteria[4,5]. Cotard's syndrome is nowadays seen as a monothematic delusion[6], a conceptualization that we consider to be erroneous, since, as Cotard described, we observed in our patient that the psychopathology of this syndrome exceeds by far the unique association with nihilistic delusions that has been emphasized in recent years. We find in our patient many similarities with the case described by Cotard 1: a) anxiety; b) ideas of condemnation; c) suicidal behavior; d) ideas of non-existence and e) delusions of immortality.

It is also interesting to observe the clinical course of this patient; starting from mild anxious-depressive affective symptoms with depersonalization and derealization, passing, after three months, by a frankly psychotic symptoms, until the development of Cotard's syndrome, to later persist with depressive symptoms. This evolution is in accordance with what was reported by Yamada et al.[7], who proposed that the evolution of Cotard's syndrome occurs in three stages: a) germination, where hypochondria, cenestopathy and depressive mood are frequently observed; b) blooming, where delusions of immortality and nihilistic, along with anxiety and negativism are seen; c) chronic, with two results, one involves a persistent emotional deterioration with a chronic change (type depressive) while the other involves the systematization of delusions (paranoid type). Graux et al.[8] theorize that hallucinations in patients with Cotard and Capgras syndrome occur when: a) they emerge spontaneously from sensory experiences after prolonged depersonalization; and b) artificially modify perceptual experiences, no longer under the usual atmospheric signals, but through strong emotional signals, being the main (and as we saw in our patient) the fear.

The nosology of this syndrome may be due to affective symptoms (psychotic depression), delusional (Cotard type I) or resulting from a combination of both (Cotard type II)[9]. This has therapeutic implications, since probably the patients with Cotard's syndrome next to delusional disorders do not adequately respond to antidepressants, as we recently reported in a patient with schizophrenia who developed this syndrome[10]. The association between Cotard's syndrome and schizophrenia may increase the risk of self-injurious behaviors[11,12]. If we use the Classification proposed by Berrios and Luque[9], our patient would belong to the Cotard type II group, due to the combination of affective and delusive symptoms. Previous reports indicate that the combination of antipsychotics and antidepressants may be useful in this type of patients[13,14]. Chou et al.[15] described a remarkable psychopathological improvement in a patient with Cotard's syndrome after two months of treatment with fluoxetine 40 mg/day and risperidone 6 mg/day. Another reported combination was venlafaxine 225 mg/day and quetiapine 600 mg/day, resulting in improvement of affective and delusional symptoms after two weeks of treatment[16]. If the affective symptoms are very intense, some authors propose the use of mood stabilizers[17,18]. There are reports of cases in which electroconvulsive therapy (ECT) treatment was successful[19,20], and it was proposed as the treatment of choice.

COMPETING INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Antipsychotic therapy amongst Cytochrome P450 2D6 poor metabolizers in the clinical practice: A case report

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Dear Editor,

Cytochrome P450 2D6 (CYP2D6) is encoded by a highly polymorphic gene, with more than 70 known alleles and over 130 genetic variations described[1]. Its expression is functionally absent in 10-20% of Caucasians[2]. Four polymorphisms (*3, *4, *5, *6) of CYP2D6 are responsible for most inactive alleles (98%) in Caucasians[3]; individuals carrying these defective alleles lack enzymatic activity and are poor metabolizers (PM) for CYP2D6 substrate drugs.

CYP2D6 is the main metabolic pathway of near 40% of antipsychotics[2]: chlorpromazine, perphenazine, haloperidol, zuclopenthixol[4], thioridazine[5] and also atypical antipsychotics, mainly risperidone, aripiprazole[6] and olanzapine[5].

It has been shown that metabolic ratio and side effects due to antipsychotics substrate to CYP2D6 can be affected by CYP2D6 genetic variants[5], resulting in a clinical association between CYP2D6 PM phenotype and antipsychotic toxicity[1]. CYP2D6 PMs show higher steady-state concentrations at a given dose of perphenazine[7], haloperidol, zuclopenthixol[8], risperidone[9] and aripiprazole[10,11]. Furthermore, they are likely to have poor tolerance for typical antipsychotics and risperidone, with average tolerance for other antipsychotics[6]. Further, patients showing this pharmacogenetics profile experience a higher rate of concentration-dependent adverse drug reactions (ADRs), mainly extrapyramidal effects[12-14] and tardive dyskinesia[15-17], implying significantly higher prevalence of non-compliance[18], higher costs and longer lengths of hospitalizations[19]. Moreover, individuals with PM CYP2D6 *3 and *4 allelic variants could also experience larger BMI increases with olanzapine treatment[20].

These genetically encoded differences in CYP2D6 enzyme activity may predict antipsychotic side-effects with higher specificity than therapeutic drug monitoring[21]. It has been estimated that pretreatment metabolic determination may decrease adverse reactions by 10-20% and improve efficacy by 10-15% (probably by increasing treatment compliance)[22].

Preliminary dosing recommendations have been made, suggesting that homozygous CYP2D6 PM patients should receive 30% of standard dose of perphenazine, 60% of olanzapine[23], half dose of haloperidol[12,24] and zuclopenthixol, maximum dose to 10mg/day of aripiprazole, and mild doses of risperidone being extra alert to ADR, or select an alternative drug such as pimozide, flupenthixol, fluphenazine, quetiapine, clozapine[25] or ziprasidone[21]. Furthermore, in other types of drugs such as SSRI, statins or anticoagulants, various guidelines and consensus documents are available about how to adjust treatment dosages depending on genotype[23,26]. However, except for a few clinical scenarios -carbamazepine in patients with Asian ancestry[27], cancer treatment, HIV and