Late paraphrenia, a revisited diagnosis: case report and literature review

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Dear Editor,

With the growing aging population, we are seeing more and more psychosis arisen for the first time in older people[1]. Late paraphrenia (LP), a concept introduced by Roth[2], is an important differential diagnosis in the schizophrenic spectrum, in the elderly. Thus, despite the lack of studies on this subject in recent decades, and the official classifications DSM-5 and ICD-10 have excluded this diagnosis, several authors argue that the LP doesn't lose its usefulness[1,3].

The observation of psychotic symptoms onset over the age of 60 years in individuals without any history of psychiatric illness has become more credible the hypothesis that LP is a disorder independent of schizophrenia[4]. Some people presenting LP have received several diagnoses, including atypical psychosis, delusional disorder, psychotic disorder not otherwise specified, schizoaffective disorder and persistent persecutory states of the elderly. More recently, LP was classified as very late-onset schizophrenia like psychosis[4,5].

The authors aim to describe a case of LP and summarize the most important aspects of this subject.

Case report

A 63 years old, caucasian, single, childless and a retired secretary woman was admitted to the psychiatric hospitalization for verbal aggressiveness towards her relatives in the context of persecutory ("my neighbors are persecuting me, they put cameras in my house") and damage ("they want to kill me... when I leave the house, they go there and poison the food... now my nephews allied to them... Lately I just realize meals at home with nearly purchase food, because this is the only way I can assure that the neighbors have no opportunity to poison me. I began to take breakfast and afternoon snack out of home because the fact that the milk package, butter, cheese, marmalade and packets of biscuits are open in the fridge or kitchen cabinets makes easy the poisoning when I am not at home") delusions, as well as auditory hallucinations ("I hear them say that they will kill me and it will not be long before that happens... they accuse me of stealing them, but it's a lie...").

Her sister and two nephews mentioned for nearly two months noticed that the patient became more suspicious than her usual and started to make more meals outside of home. Three days before, the day of her birthday, they decided to make her a surprise by appearing at her home with a cake to celebrate. However, the patient became very angry and said "I do not eat the cake; you do not think I fall into this trap, you are done with them (neighbors) to poison me..." In this context, they called an ambulance that led the patient to the emergence service, and after psychiatric assessment, she was admitted voluntarily. Her relatives denied that they had noted any patient´s cognitive and functional deterioration. They further argued that there were no precipitating existential factors for the current psychopathological condition. It was also confirmed that the paranoid ideas were delusional.

On examination, she was found alert and oriented. Appearance was clean and well groomed. Attention, concentration and memory were intact. Speech was fluent, normal in rate and volume, and there was no formal thought disorder. Mood was syntonic. No suicidal or homicidal ideation. Persecutory and damage delusions as well as auditory hallucinations. Absence of insight into the signs and symptoms of the illness, however she accepted to be hospitalized since she felt the need to be a few days far from her neighbors "to regain her strength". No changes in the sleep-wake cycle or appetite.

She had cataracts in both eyes, waiting for surgery; hearing impairment, but without the need for wear a hearing aid; and dyslipidemia, medicated with atorvastatin. There was no history of substance abuse or allergies. She had no previous history of mental illness. However, her older brother suffers from schizophrenia.

About patient´s premorbid personality, she was suspicious, unsociable, with no particular interest in the people around her, preferring to be by herself and feeling awkward when other people try to initiate a relationship. Throughout her life, she had no any love relationship neither sexual intercourse.

She was initially given paliperidone 6mg/daily and lorazepam 2mg/daily. She also attended the activities of occupational therapy. Secondary causes of psychosis were excluded from extensive physical as well as several supplementary di-

agnosis tests, which results were all negative. Such tests included analytical study with complete blood count, ionogram, renal, liver and thyroid function, vitamin B12 and folic acid assay, screening for syphilis, human immunodeficiency virus, hepatitis B and hepatitis C, summary examination of urine and dosing of substance abuse; chest x-ray, electroencephalography, electrocardiography as well as brain magnetic resonance imaging. It was also requested collaboration of neurologists, who ruled out any neurologic disturbance. The psychological evaluation showed no deficits on cognitive assessment, but high paranoid score on personality assessment.

The patient presented a progressive improvement in her clinical condition. She had a little better insight into her disorder and was calmer and less suspicious with her relatives, during the visits, who apologized for accusations, which recognized as false. However, she still had some misgivings with regard to her neighbors. Dose of anxiolytic was gradually reduced to its discontinuation. After psychopathological stabilization, and taking into account the possibility of supervision by the family, the patient was discharged from internment and referred to the outpatient psychiatric consultation, with indication for maintenance antipsychotic treatment. She has so far adhering to treatment, without relapses, however her functioning level is lower than the premorbid one.

Discussion

A likely diagnosis for this psychotic illness arising anew in this age group on a background of sensory deficits is that of LP. This condition may be the mode of presentation of schizophrenia in late life, or it may represent a distinct condition. It shares delusional beliefs and possible hallucinations with schizophrenia, but is distinguished by the well-preserved personality and affect. It has also been suggested that the older the patient, the greater are the similarities between LP and late onset schizophrenia in respect of neuropathology, treatment and prognosis. Delusions are often persecutory, although they can also be erotic, hypochondriacal or grandiose in nature. Hallucinations have been reported in visual, touch, and smell modalities, but they are usually auditory[6]. Cognitive deterioration occurs very slowly but may lead to mild dementia over several years[5]. It develops usually in the single women, socially isolated, with premorbid paranoid or schizoid personality and family history of schizophrenia. Sensory deficits are common and there is an increase in the prevalence of cerebrovascular diseases[6]. Pathological studies show the presence of neurofibrillary tangles, primarily within the entorhinal cortex, which may explain many of the symptoms in paraphrenia[5].

LP is a chronic condition requiring long-term treatment with antipsychotics, probably as a depot preparation, in order to improve compliance and thus reducing relapse rates[4,7]. Careful consideration should be given to vulnerability of the elderly to side-effects of antipsychotics. Atypical agents have become the first choice drugs in view of their better tolerability, particularly in low doses and under supervision[4]. In most cases, medication only reduces the delusions beliefs, however may allow the patient to conduct a reasonably normal life despite of it[1]. Premorbid paranoid or schizoid personality, longer duration of disorder, poor social and family support, poor adherence to therapy and underlying cerebrovascular disease have been suggested as poor prognostic factors. If associated with sensory deficits, the correction of these can improve the prognosis of LP[8]. Indeed, a multidisciplinary approach constitutes the best hope for effective treatment and outcome[6].

Despite her premorbid paranoid and schizoid traits, our patients present factors that could contribute to improving her outcome, namely relatively short duration of disorder, good family support and, so far, good adherence to therapy. Moreover, she is waiting for cataract surgery, which will constitute an important therapeutic aspect, included in an approach that is intended to be multidisciplinary.

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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

paediatric codeine[28], for which FDA recommends routine prospective pharmacogenomic testing[23], the aforementioned recommendations have not been validated by means of prospective studies, and routine genetic determinations of specific CYP2D6 genotypes has not yet been considered as a standard clinical practice, but reserved for those patients with a high clinical suspicion[1].

Clinical Case

The case of a 25-years-old man was reported. He presented no previous psychiatric diagnosis, and was admitted to our inpatient unit due to acute psychotic symptoms consisting on persecutory delusions, surveillance, control delusions with major affective and behavioural disturbances, intense emotional lability, guilt feelings, high psychomotor restlessness, insomnia and suicidal ideation in relationship with paranoid content.

Treatment was initiated with olanzapine 10 mg/day, which was stopped due to drowsiness. Afterwards, antipsychotic treatment was switched to amisulpride 300 mg/day. At the same time, the patient showed constipation, hypersalivation and somnolence. Mild clinical improvement was achieved, allowing the patient's discharge. Few days later, despite good drug compliance, he showed mutism probably associated to paranoid fear of being killed, perplexity, suspiciousness, self-referential delusional perceptions, apathy, delusional thoughts of catastrophe and insomnia, all of them leading to readmission.

Treatment was switched to paliperidone 12 mg/day, appearing bradykinesia and orthostatic hypotension with a vasovagal syncope. Further, poor clinical response was achieved after two weeks, so clozapine 100 mg/day was added to the treatment strategy. The patient also presented hypersalivation and oversedation. On the third day, he suddenly suffered from an episode of high temperature (38,3ºC), motor and consciousness disturbances including disorientation, behavioural disorganization, visual hallucinations, muscular rigidity, tremor, antigravitational posture, hypotension, sweating and mucocutaneous pallor. Osteotendinous reflexes were normal and no restlessness nor digestive symptoms were reported. Blood tests revealed slight neutrophilia (7.6·10^9/L) without leukocytosis, ALT 67 U/l [5-40], Reactive C protein 5.25 mg/dL [<1] and normal Creatinine kinases (CKs, 117 U/L). Clozapine blood levels were 416 ng/mL [Normal range: 50-700]. Urinary tests and chest X-Ray were normal. Despite normal CKs, on suspicion of a possible Neuroleptic malignant syndrome, both paliperidone and clozapine were subsequently stopped. Antipyretics and fluid therapy was supported to the patient, no antibiotic therapy was required.

Pharmacogenetic procedures were performed, searching for the following genetic variants: CYP3A4*1/*1B, CYP3A5*3/*1, CYP2D6*3/*4/*5/*6 and CYP2C19*2/*3. Single nucleotide polymorphisms (SNPs) were analysed using reverse transcription polymerase chain reaction (RT-PCR) on DNA.

Homozygous CYP2D6*4 polymorphism -PM phenotype- was revealed by pharmacogenetics study. It also showed heterozygous CYP2C19*2 polymorphism (intermediate metabolizer, not clinically significant).

A week after treatment stopping, the patient was oriented, afebrile and hemodynamically stable. However, he presented poor appetite, perplexity and monosyllabic speech. Electroconvulsive therapy (ECT) was initiated. Due to persistent delusional content and irritability, low doses of aripiprazole 10mg/day were added presenting akathisia. Progressively, more reactive mood, higher appetite and higher social interaction were observed. A total of 23 ECT sessions were required, and the patient was discharged after 3 months of hospitalization.

Conclusions

In this case, the pharmacogenetics analysis revealed a reduced enzymatic activity in CYP2D6, which is the main metabolizing pathway, together with CYP3A4, for aripiprazole, and is a secondary but significant pathway in the metabolism of olanzapine and clozapine[6]. This fact could have explained the adverse effects presented in this patient; however, there is a lack of strong evidence about dosage adjustments or therapeutic changes considering CYP2D6 status on guidelines focusing on these drugs[1].

Among patients with this pharmacogenetics profile (CYP2D6 PMs) we would suggest that, instead of risperidone, paliperidone, as already being its active metabolite (9-hydroxirisperidone), could be considered as a valid alternative, since it has scarce hepatic metabolism and its serum concentrations are not influenced by CYP26D polymorphisms[11]. Amisulpride would also be a useful strategy to consider in terms of tolerability, since its excretion is mainly by kidney[6]. However, in this case, both amisulpride and paliperidone also led to notorious side effects and poor clinical response. From our point of view, possible reasons for this fact may involve the young age of the patient[29] and the high doses of paliperidone that were used in this case, leading to side effects. Another hypothesis could be the effect of P-Glycoprotein (P-gP), an ATP-dependent efflux pump transporter, encoded by polymorphic MDR1 gene, which influences drug concentration and distribution across the blood-brain barrier[30]. Further, both antipsychotics have been found to be main substrates of P-Glycoprotein[6]. However, these allelic variations weren't studied in this patient.

The fact that treatments like paliperidone and amisulpride -which theoretically would have suited our patient's

pharmacogenetic profile- neither contributed to a significantly better tolerability, highlights the small effect that extreme genetic phenotypes may have on the metabolization of second-generation antipsychotics. CYP2D6 genotyping may be useful for pimozide, aripiprazole, risperidone and clozapine[27]; nevertheless, CYP2D6 is considered a contributory factor[14] with a limited role, and there is still a lack of evidence to support its clinical utility[31].

Accordingly, we consider that prospective randomized clinical studies are necessary to establish strong recommendations considering pharmacogenetics on atypical antipsychotics, before the concept of tailored treatment can be applied to psychopharmatherapy in the clinical setting.

Taken together, we would suggest that pharmacogenetic studies should be determined early in those patients presenting multiple side effects with various antipsychotics and high serum drug rates at standard or even low doses, with the main aim of preventing potentially severe adverse drug reactions and shorten hospitalizations. Non-pharmacological treatment as ECT, which was well tolerated in our patient, could be considered as well.

However, in the case we reported, pharmacogenetic studies were performed after various therapeutic trials and after the patient had already presented many adverse drug reactions, resulting in severe symptoms and prolonged hospitalization. In the future, pretreatment genotyping procedures could lead us to the identification of patients at risk for poor efficacy or toxicity, and may offer tools for an individualized, safer and more efficient pharmacotherapy.

CONFLICTS OF INTEREST

Laura Espinosa-Martínez, Adriana Fortea and Giovanni Oriolo have received honoraria from Lundbeck-Otsuka and Janssen. Alexandre González-Rodríguez has received honoraria or has been paid for travels from Pfizer, Janssen, Lundbeck-Otsuka and Ferrer, and received the First Juan José López-Ibor Foundation Grant for Young Researchers. Eduard Parellada has received honoraria and/or research grants from Fondo de Inverstigación Sanitaria (PI080055) of the Spanish Ministry of Science and Innovation, Fundació la Marató de TV3 of Catalonia, Janssen-Cilag, Glaxo-Smith-Kline and Ferrer.

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