

Caso clinico

Cotard's Syndrome after breast surgery successfully treated with aripiprazole augmentation of escitalopram: a case report

Sindrome di Cotard secondaria a un intervento di chirurgia al seno trattata con successo mediante augmentation con aripiprazolo dell'escitalopram: un caso clinico

DOMENICO DE BERARDIS^{1,2}, MAURIZIO BRUCCHI³, NICOLA SERRONI¹, GABRIELLA RAPINI¹, DANIELA CAMPANELLA¹, FEDERICA VELLANTE^{1,2}, ALESSANDRO VALCHERA⁴, MICHELE FORNARO⁵, FELICE IASEVOLI⁶, MONICA MAZZA⁷, GIULIANA LUCIDI⁸, GIOVANNI MARTINOTTI², MASSIMO DI GIANNANTONIO²

E-mail address: dodebera@aliceposta.it

¹Department of Mental Health, Psychiatric Service of Diagnosis and Treatment, Hospital "G. Mazzini", ASL 4, Teramo, Italy

²Department of Neuroscience and Imaging, Chair of Psychiatry, University "G. D'Annunzio", Chieti, Italy

³UOSD Senology, Hospital "G. Mazzini", ASL 4, Teramo, Italy

⁴Hermanas Hospitalarias, FoRiPsi, Villa S. Giuseppe Hospital, Ascoli Piceno, Italy

⁵Department of "Scienze della Formazione", University of Catania, Italy

⁶Laboratory of Molecular Psychiatry and Psychopharmacotherapeutics, Section of Psychiatry, Department of Neuroscience, University School of Medicine "Federico II", Naples, Italy

⁷Department of Health Science, University of L'Aquila, Italy

⁸Director, School of Nursing, MeSvA Department, University of L'Aquila, Italy

SUMMARY. In 1880 the French neurologist Jules Cotard described a condition characterized by delusion of negation (nihilistic delusion) in a melancholia context. Recently, there has been a resurgence of interest in Cotard's syndrome (CS), but the nosographical figure of CS remains unclear. It isn't determined if it pertains to the delusional themes area or if it is related to the sense of immanent ruin in some depressive episodes. For these reasons CS has recently been supposed to be an intermediate form. Furthermore, since even less is known about secondary CS in subjects who had never suffered of psychiatric disorders, in the present case we report the development of a secondary CS in a female patient who underwent a lumpectomy for the removal of a benign fibroadenoma. The patient responded well to aripiprazole augmentation of escitalopram and totally remitted.

KEY WORDS: Cotard' Syndrome, nihilistic delusion, melancholia, negation, depression, aripiprazole, augmentation, escitalopram.

RIASSUNTO. Nel 1880 il neurologo francese Jules Cotard descrisse diversi pazienti affetti da una sindrome definita *délire de négation* (delirio nichilistico) in un contesto di melanconia depressiva. Recentemente, l'interesse di molti ricercatori ha portato una nuova attenzione verso la sindrome di Cotard (CS), anche se la sua collocazione nosografica rimane dibattuta. Non è infatti ancora del tutto chiarito se essa appartenga più all'area delle psicosi deliranti o a quella dei disturbi dell'umore. Secondo alcuni autori la CS può essere considerata una forma intermedia, condividendo alcune caratteristiche sia delle psicosi deliranti sia della depressione maggiore con sintomi psicotici. Inoltre, molto meno è noto circa i casi di CS secondaria a eventi stressanti in soggetti con anamnesi psichiatrica negativa. Nel presente articolo viene infatti descritto un caso di CS in una paziente che non aveva mai sofferto di disturbi psichiatrici, sottoposta a una nodulectomia per la rimozione di un fibroadenoma benigno. La paziente fu trattata con successo mediante l'aggiunta di aripiprazolo alla terapia corrente con escitalopram.

PAROLE CHIAVE: Sindrome di Cotard, delirio nichilistico, melanconia, negazione, depressione, aripiprazolo, augmentation, escitalopram.

INTRODUCTION

In 1880 the French neurologist Jules Cotard described a condition characterized by delusion of negation with corporeal themes in a melancholia context¹. At first he formulated it as a new type of depression characterized by: anxious melancholia, idea of damnation or rejection, insensitivity to

pain, delusions of nonexistence concerning one's own body, and delusions of immortality². Cotard categorized it as *Lypémanie*, a kind of psychotic depression described by Esquirol³. In 1882, he introduced the term *délire de négations*⁴.

After some acknowledgments by Séglas⁵, Regis⁶ and Toulouse⁷, several findings, although dissonant, have succeeded especially by French clinicians who, even with critical

acumen, preferred to keep the traditional image⁸. Most recent studies about this “uncommon syndrome”, have instead considerably drifted away from them, giving new psychopathological interpretations⁹⁻¹¹.

However the nosographical figure of Cotard’s Syndrome (CS) remains unclear^{12,13}. It isn’t determined if it pertains to the delusional themes area or it is related to the sense of immanent ruin in some depressive episodes: patients that belong to both these psychotic areas may express experiences of somatic loss associated with psychomotor arrest, a kind of deep melancholic state¹⁰. For these reasons CS has recently been supposed to be an intermediate form¹⁴. Furthermore, as even less is known on secondary CS in subjects who had never suffered of psychiatric disorders, in the present case we report a development of a secondary CS in a female patient who underwent a lumpectomy for the removal of a benign fibroadenoma, successfully treated with aripiprazole augmentation of escitalopram.

CASE REPORT

A 38-year-old female white-collar married with one daughter came to our observation at the outpatient facility of Psychiatric Service of Diagnosis and Treatment of Teramo (Italy) in January 2013, referred by her primary care physician.

About seven months before our visit, the patient underwent a lumpectomy for the removal of a painful breast mass diagnosed as a benign fibroadenoma after breast biopsy. The surgical intervention was executed without pre- and post-operative problems and without leaving reliquates. The histological examination revealed no signs of a cancer. However, her husband noted that the patient immediately before the surgical intervention become more ruminative and less active, but she told him she was worried about the possibility to have a malignant tumor.

After intervention, depressive symptoms gradually manifested and worsened within one month. She refused to go to work complaining of feeling generally unwell, “stressed”, anxious, less concentrated and expressed the belief to have a malignant cancer (despite evidences) and the sensation to have a “stone in the chest”. These symptoms required consultation by her primary care physician who prescribed escitalopram up to 20 mg/day for almost five months, with modest benefits and, after, was sent us for a consultation. At our evaluation, the personal and familiar psychiatric anamnesis were negative and the patient showed depressed mood, anhedonia, loss of energy, crying spells, diminished ability to concentrate and impaired functioning.

During the visit, together with the depressive symptoms she verbalized also nihilistic delusions that were outstanding, pervasive and more severe than the depressive symptoms: «...I can’t see me in the mirror as I have no more my breast... I don’t have any more my heart and lungs, as during intervention they putrefied and were removed... My chest is empty and stoned, so I can’t feel any emotion... All my internal organs are putrefying and becoming stones...». She expressed also delusion of nonexistence: «...I don’t exist anymore as a person... I’m dead because I’ve lost my organs...», as well as delusions of immortality: «... I know that anesthesia killed me and I’m now a zombie who will eternally live in damnation...». A mild suicide ideation was reported but the patient told that «... I can’t kill myself as I will continue to live... isn’t possible to kill a dead person...».

On the basis of the Structured Clinical Interview for DSM-IV, she received a diagnosis of Major Depressive Disorder with Psy-

chotic Features. However, her depressive symptoms were moderate-severe with Hamilton Rating Scale for Depression (HAM-D) score of 25. Laboratory results, brain MRI, electroencephalogram, electrocardiogram and chest radiograph were within normal limits as well as laboratory analyses (including thyroid function, immunological parameters and cancer biomarkers). Also substance or alcohol use was ruled out as the anamnesis and laboratory screening were negative. The patient refused to be admitted in our psychiatric ward and also her husband was contrary to admission. She also refused a psychotherapy due to perceived lack of efficacy and financial hardships. However, she accepted to take medications and go back every week in our ambulatory to make a control visit. On the basis of patient clinical picture, aripiprazole 5 mg/day was introduced in addition to escitalopram. After one week of aripiprazole monotherapy, the depressive symptoms and nihilistic delusions somewhat improved (HAM-D score of 22) and aripiprazole was titrated to 10 mg/day. No adverse effects related to aripiprazole/escitalopram combination were observed during the second week and HAM-D scores further reduced to 19. At the end of fifth week, cotardian symptoms remitted and response was observed with an HAM-D score of 11. At the end of the seventh week of aripiprazole/escitalopram combination, after a gradual and continuous improvement, a full remission was obtained with a complete recovery (HAM-D score of 6). The patient was subsequently followed on a bi-weekly basis and then once monthly in our outpatient service. Escitalopram was gradually reduced to 10 mg/day after other three months of therapy without problems.

The last observation was made in October 2013: the patient was still taking aripiprazole 10 mg/day and escitalopram 10 mg/day with complete remission, without signs of cotardian delusions and/or adverse effects related to the medications. The patient provided informed consent to present this report.

DISCUSSION

In the present case report we described a patient who never suffered of psychiatric disorder and developed a secondary CS after a surgical intervention, successfully treated with aripiprazole augmentation of escitalopram.

The first evidence-based classification of CS was made by Berrios and Luque in 1995¹³. After a retrospective factorial analysis of 100 cases, they described three types: 1) Psychotic depression: included patients where overhang the picture of melancholia in comparison of nihilistic delusions; 2) Cotard type I: included patients that show a clear CS, with more prominent delusions in comparison to the depressive picture; 3) Cotard type II (mixed group): anxiety, depression, auditory hallucinations, delusions of immortality, nihilistic delusion, and suicidal behavior are the prominent features. Our patient showed characteristics compatible with a Type I CS, explaining why the clinical picture radically improved with aripiprazole augmentation.

Moreover, CS can appear after a prodromic period (germination stage) characterized by a vague feeling of anxiety, feeling of derealization and depersonalization, hypochondria and delusion of guilt^{15,16}. After this stage, the syndrome develops around three classic themes: denial of body part, delusions of immortality, *délire d’énormité* together with melancholia and ideas of damnation and possession that may increase self-aggressive behaviors¹⁷⁻¹⁹. The described patient followed these stages, but, luckily, did not showed a manifest self-aggressive behaviors.

Cotard's Syndrome after breast surgery successfully treated with aripiprazole augmentation of escitalopram

However, the problem of the present case was the development after a breast surgery in a subject without previous psychiatric problems. Several cases of secondary CS have been published and almost all evidences suggest the possibility of perceptual alterations due to central nervous system (CNS) lesions in such cases²⁰⁻²². In their comprehensive article, Debruyne et al.²³ reviewed the co-occurrence of CS with other rare psychiatric syndromes and with several organic conditions, but, in our case, all possible causes were ruled out and a diagnosis of a pure single episode Type I CS secondary to stressful life event (breast surgery) was made.

To our knowledge, there is only one published report of CS that developed after abdominal surgery²⁴. Therefore it is possible to hypothesize that surgical interventions may be a possible independent risk factor for development of CS even in healthy individuals. It should be noted, in the present case, that a breast surgery, even if not too destructive, may be particularly distressing for a young woman more than the abdominal surgery, as involves body image and self-esteem²⁵. In fact, it has been demonstrated that younger women, particularly those with poor body image, are at an increased risk for pre- and post-surgical emotional distress²⁶. Therefore, these women may benefit from pre-surgical assessment and interventions designed to improve body image or to address emotional distress and negative attributional styles that may both contribute to the development of severe depressive symptoms. In fact, the patient with CS, whose attributional style may be introjective, might interpret emotional distress and strange sensations of depersonalization or derealization in terms of a change in herself but not in the external world²⁷.

There are several reports of successful pharmacologic treatment of CS and combination strategies (antidepressants plus antipsychotics) are often used²⁸. The aripiprazole monotherapy has been used with good results in a case of CS²⁹ and was effective as augmentor in the present case, as it has been demonstrated an hyperactivity of dopamine systems in CS³⁰. The effect of aripiprazole on the dopamine systems may be attributed to its targeting of presynaptic autoreceptors and post-synaptic D2 receptors explaining why aripiprazole was effective in this case²⁹. On the other hand, as also depressive symptoms improved, it is possible that an indirect facilitation of dopamine transmission through 5-HT receptor-mediated pathways may be involved in the therapeutic response, potentiating the effect of escitalopram³¹.

In conclusion, CS may develop after breast surgery even in women who never suffered of psychiatric disorder. Therefore a pre- and post-surgical assessment of psychiatric status may be useful especially in young women who undergo breast surgery, even if not destructive. The aripiprazole add-on to antidepressant treatment may be a therapeutic option in SSRI-refractory CS, but this was only a case-report and further studies are necessary.

REFERENCES

1. Cotard J. Du délire hypocondriaque dans une forme grave de mélancolie anxieuse. *Ann Med Psychol* 1880; 4: 168-74.
2. Cotard J, Camuset M, Séglas J. Du délire des négations aux idées d'énormité. Paris : L'Harmattan, 1997.
3. Esquirol JED. Des maladies mentales considérées sous les rapports médical, hygiénique et médico-légal. Paris: Baillière, 1838.
4. Cotard J. Du délire des négations. *Archives de Neurologie* 1882; 4: 152-70.
5. Séglas J. Leçons cliniques sur les maladies mentales et nerveuses. Paris: Asselin et Houzeau, 1895.
6. Régis E. Note historique sur le délire de négation. *Gazette Médicale de Paris* 1893; 6.
7. Toulouse E. Note sur un cas de délire de négation. *Ann Med Psychol* 1893; 51: 259-70.
8. Leroux A. Actualisation clinique du délire de négation globale. *Ann Med Psychol* 1986; 144: 971-86.
9. Enoch D, Ball H. Cotard's syndrome. In: Enoch D, Ball H (eds). *Uncommon Psychiatric Syndromes*, (4th edition). London: Arnold Publishers, 2001.
10. Berrios GE, Luque R. Cotard's syndrome: analysis of 100 cases. *Acta Psychiatr Scand* 1995; 91: 185-88.
11. Pallagrosi M, Majorana M, Carlone C, et al. Sensitive delusion of reference, revisitation of a concept: clinical accounts on onset paranoid psychosis. *Riv Psichiatr* 2012; 47: 440-6.
12. Berrios GE, Luque R. Cotard's delusion or syndrome? A conceptual history. *Compr Psychiatry* 1995; 36: 218-23.
13. Bersani G. The future of depression: knowledge development, therapy evolution. *Riv Psichiatr* 2011; 46: 6-11.
14. Young AW, Leafhead KM, Szulecka TK. The Capgras and Cotard delusions. *Psychopathology* 1994; 27: 226-31.
15. Yamada K, Katsuragi S, Fujii I. A case study of Cotard's syndrome: stages and diagnosis. *Acta Psychiatr Scand* 1999; 100: 396-8.
16. Van den Eynde F, Debruyne H, Portzky M, De Saedeleer S, Audenaert K. The syndrome of Cotard: an overview. *Tijdschr Psychiatr* 2008; 50: 89-98.
17. Berrios GE, Luque R. Cotard's delusion or syndrome? A conceptual history. *Compr Psychiatry* 1995; 36: 218-23.
18. Vanni A, Biancosino B, Marmai L, et al. Psychobiological concomitants of aggressive behaviour among psychiatric inpatients: a control study. *Riv Psichiatr* 2004; 39: 40-4.
19. Sarchiapone M, Carli V, Cuomo C, et al. Interaction gene-environment in psychiatric disorders associated to suicidal behaviours: an update. *Riv Psichiatr* 2009; 43: 341-7.
20. Gardner-Thorpe C, Pearn J. The Cotard syndrome. Report of two patients: with a review of the extended spectrum of "délire des negations". *Eur J Neurol* 2004; 11: 563-6.
21. Alvarez P, Puente VM, Blasco MJ, Salgado P, Merino A, Bulbena A. Concurrent Koro and Cotard syndromes in a Spanish male patient with a psychotic depression and cerebrovascular disease. *Psychopathology* 2012; 45: 126-9.
22. Bandinelli PL, Trevisi M, Kotzalidis GD, Manfredi G, Rapinesi C, Ducci G. Chronic Koro-like Syndrome (KLS) in recurrent depressive disorder as a variant of Cotard's delusion in an Italian male patient. A case report and historical review. *Riv Psichiatr* 2011; 46: 220-6.
23. Debruyne H, Portzky M, Van den Eynde F, Audenaert K. Cotard's syndrome: a review. *Curr Psychiatry Rep* 2009; 11: 197-202.
24. Sharma V, Biswas D. Cotard's syndrome in post-surgical patients. *J Neuropsychiatry Clin Neurosci* 2012; 24: 42-3.
25. De Berardis D, Carano A, Gambi F, et al. Alexithymia and its relationships with body checking and body image in a non-clinical female sample. *Eat Behav* 2007; 8: 296-304.
26. Miller SJ, Schnur JB, Weinberger-Litman SL, Montgomery GH. The relationship between body image, age, and distress in women facing breast cancer surgery. *Palliat Support Care* 2013; 14: 1-5.
27. Ramirez-Bermudez J, Aguilar-Venegas LC, Crail-Melendez D, Espinola-Nadurille M, Nente F, Mendez MF. Cotard syndrome in neurological and psychiatric patients. *J Neuropsychiatry Clin Neurosci* 2010; 22: 409-16.

De Berardis D et al.

28. Madani Y, Sabbe BG. Cotard's syndrome. Different treatment strategies according to subclassification. *Tijdschr Psychiatr* 2007; 49: 49-53.
29. De Berardis D, Serroni N, Campanella D, Marasco V, Moschetta FS, Di Giannantonio M. A case of Cotard's Syndrome successfully treated with aripiprazole monotherapy. *Prog Neuropsychopharmacol Biol Psychiatry* 2010; 34: 1347-8.
30. De Risio S, De Rossi G, Sarchiapone M, et al. A case of Cotard syndrome: (123)I-IBZM SPECT imaging of striatal D(2) receptor binding. *Psychiatry Res* 2004; 130: 109-12.
31. De Berardis D, Serroni N, Campanella D, Moschetta FS, Ferro FM. Efficacy and tolerability of long-term aripiprazole treatment in a patient with bipolar I disorder. *It J Psychopathol* 2009; 15: 99-101.