Brief Report

Cotard's syndrome in adolescents and young adults is associated with an increased risk of bipolar disorder

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Objectives: To assess the effect of age at onset on the phenomenology of Cotard's syndrome (CS) as a recent study reported a high rate of occurrence of bipolar disorder (BD) in adolescents and young adults with CS followed up for ≥2 years.

Methods: We reviewed all cases of CS reported since it was first described. A statistical analysis was carried out to determine the effect of age at onset on CS phenomenology.

Results: We found 138 cases including 21 cases aged 25 years or younger. In these younger CS patients, BD was more frequent, and the risk of associated BD was increased 9 times ($p < 0.0001$). Within the BD sub-group ($n = 27$), admixture analysis identified two sub-groups with mean ages at onset of 18.7 years [standard deviation (SD) = 3.2] and 50.5 years (SD = 11.7).

Conclusions: Young people with CS should be monitored carefully for the onset of BD, and families should be educated about this risk. Treatment with mood stabilizers can be helpful for those who develop BD. Within BD associated with CS, early versus late onset should be distinguished.

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Cotard's syndrome (CS) is a rare state in which the central symptom is a delusion of negation. Patients suffering from the syndrome exhibit a denial that they exist or that a part of their body exists. They may also complain of damnation, possession or other delusional ideas, such as feeling enormous and immortal or that nothing exists or that another person's identity (doctor, mother) is not true (1). Cotard's syndrome generally occurs in patients suffering from major depression with psychotic features but it can also occur in patients suffering from schizophrenia or organic-mental conditions (e.g. general paralysis, epilepsy) (2). However, CS has received little attention in the literature; for example, Berrios and Luque (1995) found 100 cases
5 in a 100-year review (2). In young people, its frequency, course and pattern of associated disorders are unknown. Its occurrence in adolescent

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inpatients has been estimated to be <1 per 1000 per year (3). In 2005, we reported four consecutive cases seen at our institution and reviewed all the cases reported in young people. The most striking findings from this 110-year review were: (i) the severity of the disorder (examples included a 15-year-old boy who died of pulmonary infection during intensive care for malnutrition and a 15-year-old girl who exhibited malignant catatonia); (ii) the high proportion of patients (10 among 19) who were treated – apparently effectively – with electroconvulsive therapy (ECT), despite their young age; and (iii) the frequency of bipolar outcome during follow-up. Unexpectedly, among the 14 cases reported with follow-up ≥2 years, 13 patients (93%) exhibited a bipolar outcome (3). If such a high rate of bipolar disorder (BD) were to be confirmed, one might consider the possibility of treating all young patients with mood stabilizers. To test the hypothesis of a possible association of CS and BD in young people, we reviewed all cases reported so far and conducted a statistical analysis testing the effect of age on CS phenomenology.

Methods

We searched the MEDLINE database for all reports of CS reported since 1994 in the French and English literature using the following key words: *Cotard's syndrome* or *nihilistic delusion*. For cases reported prior to 1993, we relied on the review by Berrios and Luque (2). Using their methodology, a data sheet was used to record the following 19 variables in each report: age; sex; presence of anxiety; depression; nihilistic delusion [concerning the subject's body or existence or other nihilistic delusions ('conceptual'), such as 'nothing exists' or denial of others' identity]; delusions of hypochondriacal concern; immortality; guilt or damnation; other delusions; visual and auditory hallucinations; negativism; suicidal ideas; and presence of organic brain disorder (as diagnosed by the original authors). Cotard's syndrome was confirmed by the presence of delusions of negation. Two experienced psychiatrists diagnosed each case independently and reached a consensus primary diagnosis of major depression, bipolar affective disorder, schizophrenia, organic disorder or other. Cases reported before 1993 were rated by GB and RL using DSM-III-R criteria; cases reported after 1994 were rated by DC and CS, or DC and DP using DSM-IV criteria.

To test our hypothesis, the following analyses were conducted. We divided the sample into two groups: adolescents and young adults (≤25 years) and adults (>25 years). A logistic regression was then performed to test whether there was an increased risk of BD in the younger group. Finally, admixture analysis was used to determine the best fitting model for the age at onset in BD with CS. Given the literature (4, 5), we hypothesized a model with two or three sub-groups including one for adolescents and young adults.

Results

We found 33 new reports of cases of CS published since 1994 (6–38). One report (32) gave insufficient clinical data and 6 others were not considered because they were not written in English or French (33–38). The 26 new reports (6–31) that were eligible for this review included 38 new cases of CS reported since Berrios and Luque published their report (2). Therefore, the sample included 138 patients (94 females and 44 males). Mean age at onset was 47.7 years [standard deviation (SD) = 17.8 years, range 10–82 years]. The delusions of negation in these patients included denial of the existence of parts of the body in 114 cases (82.6%), of the patient's existence in 94 (68.1%), and other themes of negation in 26 (18.8%). Age, gender and diagnoses are listed in Table 1.

Comparison of the two sub-groups (≤25 years versus >25 years) showed significant differences for only 3 variables. Adults had more delusions of hypochondriacal concern (15% versus 57%, $\chi^2 = 12.2$, df = 1, p = 0.0005), whereas adolescents and young adults had more negativism (50% versus 19%, $\chi^2 = 8.6$, df = 1, p = 0.0034) and associated BD (57% versus 13%, $\chi^2 = 22.2$, df = 1, p < 0.0001). Independent predictors of BD were identified using stepwise multivariable logistic regression. Variables included in the model were

Table 1. Age, gender and diagnosis of the 138 patients with Cotard's syndrome reported from 1880 to 2005

Characteristic	n (%)
Age, years, mean (± SD) [range]	47.6 (± 17.8) [10–82]
Gender	
F	94 (68%)
M	44 (32%)
Gender of patients ≤25 years	
F	15 (71%)
M	6 (29%)
Diagnosis	
Depression	79 (57.2%)
Bipolar depression	27 (19.6%), including 22 (81%) F
Schizophrenia	14 (10.0%)
Organic	17 (12.3%)
Other	1

SD = standard devaition; F = female; M = male.

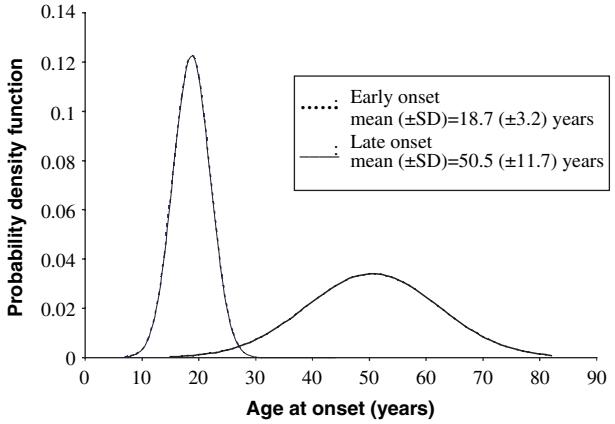

Fig. 1. Theoretical distribution of ages at onset for 27 patients with Cotard's syndrome associated with bipolar disorder in two subgroups with early and late onset.

univariate predictors with $p < 0.10$ (age, hypochondria, negativism and sex). Multivariable analysis showed that only age could predict associated BD. An odds ratio of 9 (3.27–25.15) was observed for the risk of associated BD in adolescents and young adults versus adults with CS ($p < 0.0001$).

Finally, as other reports have shown that there may be distinct age-at-onset sub-groups among bipolar patients (4, 5), we conducted an admixture analysis to test whether the observed distribution for age at onset of BD in patients with CS ($n = 27$) was a mixture of Gaussian distributions. The likelihood ratio test indicated that the model with 2 distributions fit the observed distribution of age at onset significantly better than the model with 1 distribution ($\chi^2 = 19.6$, $df = 3$, $p = 0.0002$). No further improvement was obtained with a 3-component model. The mean ages estimated in this model were 18.7 years (SD = 3.2) and 50.5 years (SD = 11.7) (Fig. 1).

Discussion

This study has several important limitations. First, the analyses pooled all reported cases of CS reported so far. In consequence, analyses were drawn on uncontrolled retrospective data. Second, CS is a rare syndrome so that there are no reported series of cases that can be compared. Third, although cases reported over a long period of time (1880–2004) were reviewed, we cannot exclude publication bias (e.g. reporting because of young age, bipolar course, or the use of ECT).

For practitioners treating depressed young people, predictors of BD are urgently needed. Studies to date have suggested several predictors, including: a rapid onset; psychomotor retardation; mood-congruent psychotic features; a family history of BD; and pharmacologically induced hypomania (39–42). In a previous report, we found that, among the 14 cases of CS in young subjects reported with a follow-up of ≥2 years, 13 patients exhibited a bipolar outcome (3). This high rate (93%) suggested that systematic therapy with mood stabilizers might be considered for prevention of mood switches after acute CS treatment in adolescents and young adults. This rate is much higher than the 28% rate of bipolar outcome that has been reported for adolescents with psychotic depression (40). Given the limitations of our retrospective study, it would be premature to recommend routine mood stabilizer treatment in young CS patients until the onset of mania, because these drugs do have adverse effects, and it would be difficult to decide when to stop mood stabilizer treatment if no manic or hypomanic episodes were ever observed. However, young CS patients should be closely followed clinically for subsequent onset of mania, and patients and their family members should be educated about the risk of BD, its symptoms and available treatments.

The results of the current study provide further evidence that the phenomenology of CS is age-related. The odds ratio for development of BD is 9 for adolescents and young adults versus adults with CS. Furthermore, in CS patients, sub-groups with early versus late onset can be distinguished statistically (Fig. 1), which supports the evidence reported by other groups that there may be a distinct BD sub-group with earlier age at onset (4, 5). Similarly, our results show that young patients with CS and BD should be distinguished from older ones.

Cotard's syndrome is a rare but severe condition, and we analyzed all the cases reported so far. Although our study has some limitations (retrospective analysis of case reports, no prospective design, small number of BD cases), our results, together with the frequency of bipolar outcome (3), support the proposition that young people with CS should be carefully monitored for subsequent onset of mania, and should be educated about the risk of BD and about its symptoms and treatment. Mood stabilizers may prevent the emergence of affective switches in those who develop BD.

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