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## Medical and developmental risk factors of catatonia in children and adolescents: A prospective case–control study

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## ABSTRACT

*Context:* Rare diseases have been associated with more and more genetic and non genetic causes and risk factors. But this has not been systematically assessed in catatonia, one of the psychiatric syndromes, that is most frequently associated with medical condition.

*Objective:* We sought to assess the medical and developmental risk factors of catatonia in children and adolescents.

*Methods*: From 1993 to 2009, 58 youths aged 10 to 18 years were prospectively admitted for catatonia and were followed up after discharge. A multidisciplinary approach assessed patients' medical condition and developmental history. A causality assessment scored medical risk (maximum score = 10;  $\kappa$  = 0.91). We compared the prevalence of catatonia in these patients to that of 80 inpatients with bipolar I disorder admitted from 1993 to 2003 who were also followed up.

*Results*: We found that 13 (22.4%) patients had medical conditions and 18 (31%) had a history of developmental disorder in the catatonia group, whereas 1 (1.3%) and 17 (22.6%) patients had the same conditions in the bipolar group (p<0.001; p = 0.17, respectively). Medical conditions associated with catatonia included auto-immune encephalitis (systemic lupus erythematosus [N=3] and anti-NMDA-receptor encephalitis (N=1), seizures (N=1), ciclosporin encephalitis (N=1), post hypoglycaemic coma encephalitis (N=1), and genetic or metabolic conditions (chorea [N=2], 5HT cerebrospinal fluid deficit [N=1], storage disease [N=1], fatal familial insomnia [FFI; N=1], and PRODH mutations [N=1]). Six patients responded to a specific treatment approach related to their medical condition (e.g., plasma exchange in the case of auto-immune encephalitis).

*Conclusion:* Catatonia in children and adolescents is associated with a high prevalence of medical conditions. This needs to be acknowledged as it may greatly delay the treatment of catatonia and the diagnosis of medically related catatonia. Tragically, this may deny patients treatment opportunities.

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## 1. Introduction

Catatonia is among the most severe psychiatric syndrome. The prevalence of catatonia in adult inpatients ranges from 7.6% to 38%. Catatonia is more frequent among women and its most commonly associated psychiatric diagnosis is mood disorder (Taylor and Fink, 2003). Catatonia has not been fully investigated in children and adolescents, although it can occur in children and adolescents. In this age

\* Corresponding author. *E-mail address:* david.cohen@psl.aphp.fr (D. Cohen). group, catatonia is rare, and it increases the risk of premature death (including suicide) by 60-fold, making it the most severe psychiatric condition (Cornic et al., 2009). The prevalence of catatonia in children and adolescent inpatients is estimated to range from 0.6% to 17.7% according to different inclusion criteria (e.g., general psychiatric unit vs. adolescents receiving electroconvulsive therapy (ECT); high income vs. low income country inpatient unit) (Cohen et al., 2005). In contrast to adult catatonia, catatonia in children and adolescents is more frequent in boys than in girls (Cohen et al., 2005; Thakur et al., 2003). The most commonly underlying psychiatric disorder is schizophrenia (Cohen et al., 2005; Takaoka and Takata, 2003), but it can also occur in youths with a history of developmental disorder (e.g.,

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pervasive developmental disorder [PDD] or intellectual disability [ID]) (Dhossche et al., 2006; Wing and Shah, 2000). Gender difference between paediatric and adult catatonia can be explained by gender differences in underlying psychiatric disorders (early onset schizophrenia is more frequent in boys and mood disorders are more frequent in women). However, the clinical presentation of paediatric catatonia is similar to that in adults, which involves psychological symptoms (e.g., mutism and social withdrawal) and motor symptoms (e.g., stupor and waxy flexibility). These symptoms can be continuous or discontinuous. Symptomatic treatments are also similar to that in adult catatonia. The first line of treatment is high doses of benzodiazepines (e.g., lorazepam≤15 mg/day). In cases of resistant or malignant catatonia, electroconvulsive therapy (ECT) is recommended, even in patients with PPD or ID (Taylor and Fink, 2003; Wachtel et al., 2008). In addition, clinical practice depends on the possibility of curing the underlying condition. Indeed, catatonia may occur in patients with various psychiatric disorders (usually schizophrenia and severe mood disorders) and medical conditions (e.g., neurological conditions, intoxication, auto-immune diseases, and metabolic conditions) (Cottencin et al., 2007; Lahutte et al., 2008). Some of these conditions have poor prognoses and may result in death (Dimitri et al., 2006). Recognising underlying medical conditions is essential because it may lead to a cure. Given the variety of possible medical conditions, guidelines have been proposed to help clinicians challenged by this complex issue (Lahutte et al., 2008).

Since 1993, we prospectively followed up a sample of youths with catatonia to investigate their socio-demographic characteristics, symptomatologies, psychiatric and medically associated conditions, developmental histories and outcomes (Cohen et al., 1999; Cohen et al., 2005; Cornic et al., 2009). This study aimed to: (1) assess the prevalence of medical risk factors and developmental histories in this sample of patients with catatonia; (2) compare it with the prevalence of medical risk factors and developmental histories found in a sample of inpatients with bipolar I disorder; and (3) assess whether socio-demographic or clinical characteristics help distinguish catatonia associated with medical/developmental risk factors from catatonia with no such risks.

## 2. Methods

#### 2.1. Patient recruitment

We assessed all patients admitted to the Department of Child and Adolescent Psychiatry at University Hospital La Pitié-Salpêtrière between 1993 and 2009 for catatonia. In all, we hospitalised 5532 patients aged 4 to 18 years. To obtain a diagnosis of catatonia, patients must present at least two motor symptoms or one motor symptom and a non-motor symptom indicative of severe behavioural and emotional impairment. The catatonia symptom list (see Supplementary Table 1) was based on the modified version of the Bush and Francis scale (Bush et al., 1996; Cohen et al., 1999; Cohen et al., 2005; Ey, 1950). We excluded patients who presented extrapyramidal syndrome secondary to antipsychotic symptoms from participation. Recruitment details are available in previous publications (Cohen et al., 2005; Cornic et al., 2007; Cornic et al., 2009). During the inclusion period, previous reporting created more attention and interest for the syndrome leading to a higher frequency of recruitment due to transfer from other French units after 2006 (40 vs. 18 inclusions, respectively). This corresponds to the opening of the French National Centre for Psychiatric Rare Diseases and Catatonia in the Department of Child and Adolescent Psychiatry at University Hospital La Pitié-Salpêtrière. We included 58 patients in this sample, aged from 9 to 18 years. Follow up clinical data of a sub-sample have been previously published (Cornic et al., 2009). Here we focused on medical conditions and developmental history.

We compared patients' prevalence of medical conditions and their developmental histories to those of a control sample of 80 inpatients with type I bipolar disorder (BP) hospitalised in the same department between 1993 and 2003. We followed up this sample between 2005 and 2006. Brunelle et al. provide a detailed description of the control sample (Brunelle et al., 2009). Forty-nine (61.3%) control youths were hospitalised for a manic episode; 31 (38.7%) was hospitalised for a mixed episode. We excluded 5 patients from the control group because they had a catatonic episode associated with BP. The local Ethics Committee approved this study.

#### 2.2. Patient assessment

We conducted a systematic assessment within the patients' first week of admission, and repeated this assessment at discharge and follow-up. This assessment included: (i) socio-demographic data (age, sex, origin and family social-economic status; SES); (ii) a semi-structured interview to evaluate patients' personal and family histories of psychiatric and medical disorders (detailed in (Taieb et al., 2002)); (iii) a clinical examination; (iv) the modified version of the Bush and Francis scale to test for the presence and severity of catatonic symptoms (Bush et al., 1996; Cohen et al., 1999; Cohen et al., 2005; Ey, 1950); (v) the Clinical Global Impression–Severity scale (CGI-S) (Guy, 1976) and the Global Assessment Functioning scale (GAF) to assess patients' clinical severity at admission and discharge; and (vi) the duration of the psychiatric episode, the duration of hospitalisation, the type of catatonia onset (e.g., <10 days = acute;  $\geq$  10 days = insidious), the duration of acute catatonia, and the type of catatonia (e.g., episodic or chronic). We considered catatonia as chronic if the patient had catatonic symptoms after discharge from the index episode. All but 7 patients had a follow up visit at least 6 months after discharge assessment (Endicott et al., 1976).

We diagnosed psychiatric conditions associated with catatonia according to DSM-IV criteria. The Diagnostic Interview for Genetic Studies (DIGS) version 2.0, a semi-structured diagnostic interview developed by the Human Genetics Initiative of the National Institute of Mental Health, assessed lifetime and current psychiatric diagnoses (www.nimhgenetics.org; French translation by CL) (Nurnberger et al., 1994). The DIGS elicits information necessary to diagnose psychotic, mood, anxiety, substance use and eating disorders as well as suicidal behaviours using the DSM-IV criteria. We interviewed most patients after the acute phase of their illness. To maximise the accuracy of our psychiatric diagnoses, we obtained clinical information from each patient's regular psychiatrist. Based on all available information, the consensus reached by the patient's treating clinician, the DIGS interviewer and one additional child/adolescent psychiatrist (DC or AC) diagnosed patients. In cases of ID or PDD, we confirmed diagnoses using the parental Autism Diagnostic Interview-Revised (Lord et al., 1994) and the Wechsler Intelligence Scales. Both scales are used routinely in the department. If we confirmed an ID or PDD diagnosis, a geneticist performed a systematic clinical and molecular evaluation including karyotype and search for 22q11 and 15q11-q13 chromosomal abnormalities by FISH in all patients, and search for Fragile X in boys (if the patient had never had this procedure performed).

## 2.3. Medical condition search

To maximise the accuracy of medical diagnoses, an internist and a neurologist performed an additional physical examination on all patients. In previous reports, we proposed guidelines for clinical and para-clinical investigations to help determine the medical conditions associated with catatonia (Lahutte et al., 2008; Sedel et al., 2007). Determining a medical condition from somatic and psychiatric examinations does not occur immediately because pathognomonic symptoms are rare and catatonia is occasionally isolated. Some symptoms must be actively searched for to orient a diagnosis. We used a multidisciplinary approach with the same medical staff during follow-up. Neurological, global examinations and psychiatric assessments were performed to A. Consoli et al. / Schizophrenia Research 137 (2012) 151–158

identify medical conditions. Even if no clinical symptoms (other than catatonia) were present, para-clinical investigations included: routine haematological and biochemical tests, antinuclear antibodies, ammoniemia, homocysteinemia, plasma ceruleoplasmine level and urinary drug screening, brain MRI and electroencephalography (EEG). Lahutte et al. provide a detailed list of these procedures (Lahutte et al., 2008). When fever was present, we performed cerebrospinal fluid analysis. Other specific investigations were performed under prescription when we found other conditions suggestive of medical or neurological problems.

#### 2.4. Causality assessment method

To assess the causality of the medical risk factors associated with catatonia, we constructed a causality assessment score (CAUS), which follows the principals of adverse medical effect assessment with standardised methods (Begaud et al., 1985; Naranjo et al., 1981). For each patient who we suspected of having a medical condition, we systematically searched for and scored the following five causality-support criteria on a 3-point scale (0 = absent; 1 = moderate; 2 = high): (1) the existence of similar cases in the literature; (2) the presence of clinical symptoms; (3) the presence of biological symptoms; (4) the presence of other para-clinical symptoms; (5) response to a specific treatment related to the suspected medical condition (e.g., improvement of catatonia after antiepileptic medication in case of seizures). With this procedure, CAUS maximum score was 10. Two raters independently scored the patients. The inter-rater reliability was excellent (2 raters, 13 cases; intraclass correlation coefficient = 0.91, [95% confidence interval = 0.86-0.99]).

## 2.5. Statistical analyses

We processed the data using R version 2.10. For all tests,  $\alpha = 0.05$ . We computed descriptive statistics for sociodemographic and clinical characteristics. Because the variable distribution was skewed and there was variance heterogeneity between groups, we used non-parametric univariate analyses to compare youths with catatonia to youths with BP: Fisher's exact test for dichotomous variables and the Mann–Whitney's *U* test for continuous variables. To compute comparisons between groups, we excluded the 5 patients that exhibited bipolar disorder and catatonia.

To assess whether underlying conditions influenced catatonia, we divided the sample into 3 groups according to patients' medical condition, history of developmental disorder, or neither (see Fig. 1). Developmental disorder was defined by the presence of PDD, ID, or a neurodevelopmental malformation. Two patients had both medical and developmental histories; we included these patients in the medical condition group. Because of the data distribution mentioned above, we compared quantitative variables using the nonparametric Kruskal-Wallis test. When the difference was significant, we conducted a subgroup analvsis using the Mann–Whitney's U test with a Holm's correction to control inflation risk of the first kind. We analysed GAF scores at discharge with an ANCOVA after adjusting for these scores at admission. We compared qualitative variables using Fisher's exact test. In the case of a significant interaction, we analysed standardised Pearson residuals to clarify the influence of each group. We calculated the odds ratios and 95% confidence intervals for binary variables.

## 3. Results

#### 3.1. The prevalence of medical risk factors in youths with catatonia

We prospectively included 58 patients with catatonia in the 1993 to 2009 cohort. Table 1 summarises the socio-demographic characteristics. Mean age at admission was 15 ( $\pm$ 1.8) years [range: 9–18]. The sex ratio was 2 males for 1 female. All but 3 patients were postpubescent. SES varied greatly among participants; 60.3% of the patients were off high and middle SES. There were no significant



**Fig. 1.** Flow chart of the study.Two patients had both medical and developmental histories; we included these patients in the medical condition group.

demographic differences among the BP sample except for age and sex ratio. Patients with catatonia were severely impaired at admission (mean CGI-S = 6.6; mean GAF = 18.9). Although patients with BP also had severe scores at admission, they were significantly less impaired compared to those of patients with catatonia. Similarly, patients with catatonia were significantly more impaired than patients with BP at discharge after adjusting for CGI-S and GAF scores at admission (Table 1).

Psychiatric diagnoses associated with catatonia included: major depressive episode (N = 18; 31% of patients), manic episode (N = 6; 10.3% of patients), brief psychotic episode (N = 3; 5.2% of patients), and schizophrenia (N = 34; 58.6% of patients). Onset was insidious in 26 patients (44.8%) and sudden in 32 patients (55.2%). The mean ( $\pm$  SD) Catatonia Rating Scale score was 20.7 ( $\pm$  5.8). All patients presented at least 5 symptoms according to the modified Bush and Francis scale.

In the catatonic group, 13 patients (22.4%) had a medical condition and 18 (31%) had a history of a developmental disorder. Although these prevalence rates are higher than those found in the BP

#### Table 1

Socio-demographic characteristics, prevalence of medical condition and developmental history in children and adolescents hospitalised for catatonia versus bipolar I disorder.

|  | Catatonia<br>(N=58)   | Bipolar I disorder<br>(N=75)   | Р   |
|--|---|--|---|
| Socio-demographic characteristics<br>Mean age (±SD)<br>Sex<br>SES: middle/good: N (%)<br>Migrant mother: N (%)<br>Migrant father: N (%)  | 15 (±1.8)<br>19 F, 39 M<br>35 (60.3)<br>33 (57)<br>31 (53)  | $\begin{array}{c} 16 \ (\pm 1.89) \\ 41 \ F, 34 \ M \\ 47 \ (62.6) \\ 41 \ (54.6) \\ 45 \ (60) \end{array}$            | <b>0.0193</b><br><b>0.0142</b><br>0.7150<br>0.837<br>1                        |
| Clinical characteristics<br>CGI-S admission: mean $(\pm$ SD)<br>GAF admission: mean $(\pm$ SD)<br>GAF discharge: mean $(\pm$ SD)<br>Medical condition N (%)<br>Developmental history N (%) | $\begin{array}{c} 6.6 \ (\pm 0.8) \\ 18.9 \ (\pm 8.6) \\ 51.5 \ (\pm 14) \\ 13 \ (22.4) \\ 18 \ (31) \end{array}$ | $\begin{array}{l} 5.96 \ (\pm 0.7) \\ 23.3 \ (\pm 7.8) \\ 63.7 \ (\pm 18) \\ 1^{a} \ (1.3) \\ 17 \ (22.6) \end{array}$ | < <b>0.001</b><br><b>0.0024</b><br>< <b>0.001</b><br>< <b>0.001</b><br>0.1659 |

SES = socio-economic status; CGI-S = Clinical Global Impression-Severity; GAF = Global Assessment Functioning.

<sup>a</sup> The patient presented an episode of mania associated to a lupus erythematosus and was treated with valproate, prednisone and telegine.

group (Table 1), the difference was only significant for medical condition:  $p = 3.8 \times 10^{-5}$ , odds ratio = 0.042, [95% confidence interval: 0.002–0.287]. Medical conditions were 24 times more likely in young patients with catatonia compared to those with BP. Among the 18 patients with catatonia and a developmental disorder, 12 patients (20.7%) had PDD, 8 patients (13.8%) had an ID, and 2 patients (3.4%) had a neurodevelopmental malformation (e.g., lumbosacral agenesis and syringomyelia). Of note, 6 patients had multiple developmental disorder diagnoses.

## 3.2. Medical conditions associated with catatonia

Table 2 summarises the medical conditions found in this series, the different clinical, para-clinical and therapeutic symptoms that support a causal relationship for catatonia, as well as the CAUS calculated for this study. Four patients presented an autoimmune encephalopathy: 3 with systemic lupus erythematosus and 1 with anti-NMDA-receptor encephalitis. In addition to specific autoimmune testing, patients showed positive responses to plasma exchanges and immune-suppressive treatments. Three patients exhibited encephalopathies of other origins, including (i) side effects from a ciclosporin treatment of autoimmune hepatitis (Begaud et al., 1985; Naranjo et al., 1981); (ii) epilepsy (behavioural symptoms: eyes fixed open, elevated arms, swaying and respiratory problems with co-occurring EEG markers: overloaded slow plots with an episode of small repetitive spikes followed by 20 s of slow delta waves repeated at 1 Hz for 10 s) that showed a good clinical response to antiepileptic medications; and (iii) a post-hypoglycaemic coma related to an insulin overdose suicide attempt in a diabetic adolescent. Five patients had a genetic or metabolic diseases, including chorea (e.g., Huntington's disease [N = 1] and unknown origin [N = 1]), FFI with positive molecular diagnosis (N=1) (Dimitri et al., 2006), storage disease (N=1); the origin of this disease is unknown because the family refused additional molecular investigations), and moderate hyperprolinemia due to 4 missense mutations of the PRODH gene (N = 1). We investigated the last patient because his symptoms resisted to benzodiazepine and only moderately improved with ECT. Of the missense mutations (i.e., P406L, R431H, Q19P, and R185W), P406L severely reduced POX activity more than 70%; furthermore, Q19P and R185W moderately reduced POX activity 30%-70% (Bender et al., 2005). Localisation of these mutations to assess their homozygosity was not possible because both parents were deceased. Finally, a systematic cerebrospinal fluid (CSF) search revealed a CSF-serotonin deficit in a 17-year-old patient. Its clinical presentation (e.g., headache and confusion) led us to actively search for a medical cause and perform a lumbar puncture in the absence of a fever. CAUS scores ranged from 5 to 10 (mean  $(\pm SD) = 7.54(\pm 1.8)$ ). Three patients had CAUSs less than or equal to 5 (see Table 2).

# 3.3. Associated variables with medical and developmental risk factors in patients with catatonia

We distributed patients into 3 distinct groups: patients with catatonia due to a medical condition (N = 13), patients with catatonia due to a developmental disorder (N = 16; excluding the 2 patients who had medical conditions and developmental histories) and patients with no medical condition or developmental disorder (N = 29). There were no differences between the 3 groups regarding sociodemographic data. A few differences emerged regarding clinical characteristics (Table 3). Insidious onset was significantly higher in patients with a developmental disorder compared to the other groups (p = 0.008). Patients with a medical condition were less likely to be diagnosed with schizophrenia than were patients in the other groups (p = 0.025). Regarding the symptoms of catatonia, echopraxia and automatic compulsive movements were more common in patients with a developmental disorder (p = 0.012). Given these signs overlap in the two syndromes (PDD and catatonia), this is not surprising.

## 4. Discussion

Considering that this sample was based on young patients who were consecutively hospitalised in a psychiatric ward due to catatonia, the most important result is that 22.4% of the patients presented a medical condition. This risk was significantly higher compared to a sample of inpatients with BP. In contrast, a high prevalence of developmental disorders was also found in patients with BP. This result corroborates a previous review specifying the kinds of medical conditions that are associated with catatonia in young people (Lahutte et al., 2008). Furthermore, the previous report recommended treating patients with catatonia using a multidisciplinary approach of psychiatrists, internists and neurologists during inpatient stay and followup; note that we located patients' medical conditions thanks to this multidisciplinary approach. Locating the medical causes of catatonia was difficult not only because of its clinical characteristics (e.g., mutism/stupor) but also because other clinical symptoms are often secondary (e.g., neurological signs). This difficulty was the case for anti-NMDA-receptor encephalitis (the ability to search for this condition has only been available in France since 2007) and most of the genetic/metabolic conditions for which confirmatory diagnoses usually occurred at follow-up. The initial clinical presentation of catatonia frequently hid the ultimate medical diagnosis. For example, mutism, motor symptoms, social withdrawal and other catatonic symptoms made clinical examinations difficult. Of these 13 patients, the link between catatonia and an underlying medical condition was not conclusively found in 3 patients (CAUS = 5). However, after removing these cases, the prevalence of medical risk factors remained high (17.2%) and significantly different from patients with BP  $(\chi^2 = 10.02; df = 1; p = 0.001).$ 

## 4.1. Medical conditions

The list of medical conditions found in this study is similar to Lahutte et al.'s (Lahutte et al., 2008) literature review, which distinguished among causes of catatonia: infectious disorders, neurological conditions, toxic states and genetic conditions from each other. The lack of infectious diseases and ecstasy abuse in our sample is probably due to two recruitment biases: (1) most patients with fever are referred to a paediatric setting (Breakey and Kala, 1977; Unni et al., 1995), and (2) the catatonia associated with ecstasy abuse is brief and usually requires intensive care because of electrolytic dysfunction (hyponatremia) (Masi et al., 2002; Maxwell et al., 1993). Neurological conditions included encephalopathies of various origins. In these cases, an etiological diagnosis is crucial because specific treatments may be required (e.g., autoimmune encephalitis). Numerous cases of catatonia in young people with systemic lupus erythematosus or with paediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS) have been reported (Elia et al., 2005; Lanham et al., 1985; Perisse et al., 2003). The pathogenic role of NMDA-receptor antibodies recently described by Dalmau et al. requires additional research (Dalmau and Bataller, 2007; Dalmau et al., 2008; Dalmau et al., 2011). Since this seminal report, however, several cases of anti-NMDA-receptor encephalitis in patients with catatonia (and other acute psychiatric features) have been reported (Consoli et al., 2011; Florance et al., 2009; Lee et al., 2006; Schimmel et al., 2009). In the future, we plan to systematically search for NMDA-receptor antibodies in the CSF of patients with an acute presentation of catatonia and EEG indicators of encephalopathy, subtle neurological symptoms or resistances to treatment. Two other patients with encephalopathies due to epilepsy or chronic ciclosporin treatments have already been reported in the literature (Primavera et al., 1994; Taque et al., 2004). An additional patient had catatonia

| Diagnostic     Sex     Age     Catatonia     Psy       Auto immune diseases     F     17     Acute malignant     Ma       Anti-INMDA     F     17     Acute malignant     Ma       Anti-INMDA     F     17     Acute malignant     Ma       Ireceptor     catatonia     fea       nccephalitis     F     15     Acute stuporous     ME       Lupus erythematosus     F     15     Acute stuporous     ME       Lupus erythematosus     F     15     Acute stuporous     ME       Lupus erythematosus     F     16     Acute stuporous     ME       Iupus erythematosus     F     16     Acute stuporous     Ob       Iupus erythematosus     F     16     Acute stuporous     Ob       In   | Psychiatric<br>diagnosis<br>Mania with psychotic<br>features<br>MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>obsessive- | Clinical arguments<br>Acute: stereotyped movements,<br>ptosis, myosis, epilepsy, ataxia<br>Post: frontal syndrome, memory<br>impairment<br>Medical history of LED<br>Impaired general health, multi<br>systemic manifestations<br>Medical history of LED | Biological arguments<br>Anti-NMDA receptor<br>antibodies: highly<br>+ in blood and CSF<br>Anaemia Coombs: +<br>Antendes: + (antinuclear,<br>anti DNA, antinucleosome,<br>anticardiolipin, anti SSA,<br>SM, ribosomal P)<br>Anaemia, neutropenia,<br>antibodies: +<br>(antinucleosome,<br>anticardiolipin anti-RNP,<br>anti Sm), complement decline | Paraclinical arguments<br>EEG +<br>PET SCAN +<br>None | Therapeutic<br>arguments<br>Effican of vacana | CAUS |
|---|--|--|--|---|---|------|
| Auto immune diseases     F     17     Acute malignant     Mathematica       Anti-INMDA     F     17     Acute malignant     Mathematica       receptor     catatonia     fea       encephalitis     F     15     Acute stuporous     MI       Lupus erythematosus     F     16     Acute stuporous     MI       Lupus erythematosus     F     9     Acute stuporous     MI       Introgenic encephalopathy     F     9     Acute stuporous     MI       (ricksnorin)     Catatonia     Cortatonia     An </th <th>Mania with psychotic<br/>features<br/>MDE with psychotic<br/>features<br/>MDE with psychotic<br/>features<br/>MDE with psychotic<br/>features<br/>Obsessive-</th> <th>Acute: stereotyped movements,<br/>ptosis, myosis, epilepsy, ataxia<br/>Post: frontal syndrome, memory<br/>impairment<br/>Medical history of LED<br/>Medical history of LED</th> <th>Anti-NMDA receptor<br/>antibodies: highly<br/>+ in blood and CSF<br/>Anaemia Coombs: +<br/>Antibodies: + (antinuclear,<br/>anti DNA, antinucleosome,<br/>anti-ardiolipin, anti SSA,<br/>SM, ribosomal P)<br/>Anaemia, neutropenia,<br/>antibodies: +<br/>(antinucleosome,<br/>anticardiolipin anti-RNP,<br/>anti STM), complement decline</th> <th>EEG +<br/>PET SCAN +<br/>None</th> <th>Efficient of market</th> <th></th>  | Mania with psychotic<br>features<br>MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>Obsessive-                             | Acute: stereotyped movements,<br>ptosis, myosis, epilepsy, ataxia<br>Post: frontal syndrome, memory<br>impairment<br>Medical history of LED<br>Medical history of LED  | Anti-NMDA receptor<br>antibodies: highly<br>+ in blood and CSF<br>Anaemia Coombs: +<br>Antibodies: + (antinuclear,<br>anti DNA, antinucleosome,<br>anti-ardiolipin, anti SSA,<br>SM, ribosomal P)<br>Anaemia, neutropenia,<br>antibodies: +<br>(antinucleosome,<br>anticardiolipin anti-RNP,<br>anti STM), complement decline                      | EEG +<br>PET SCAN +<br>None                           | Efficient of market                           |      |
| Anti-NMDA     F     17     Acute malignant     Ma       receptor     catatonia     fea       upus erythematosus     F     15     Acute stuporous     ME       Lupus erythematosus     F     16     Acute stuporous     ME       Cupus erythematosus     F     16     Acute stuporous     ME       Lupus erythematosus     F     16     Acute stuporous     ME       Lupus erythematosus     F     16     Acute stuporous     ME       Euleptic encephalopathy     F     9     Acute stuporous     Ob       Epileptic encephalopathy     F     14     Acute stuporous     Ob       Ciclosnorin     F     14     Acute stuporous     ME   | Mania with psychotic<br>features<br>MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>Obsessive-                             | Acute: stereotyped movements,<br>ptosis, myosis, epilepsy, ataxia<br>Post: frontal syndrome, memory<br>impairment<br>Medical history of LED<br>Impaired general health, multi<br>systemic manifestations<br>Medical history of LED                       | Anti-NMDA receptor<br>antibodies: highly<br>+ in blood and CSF<br>Anaemia Coombs: +<br>Antibodies: + (antinuclear,<br>anti DNA, antinucleosome,<br>anti-articolipin, anti SSA,<br>SM, ribosomal P)<br>Anaemia, neutropenia,<br>antibodies: +<br>(antinucleosome,<br>anticardiolipin anti-RNP,<br>anti STM), complement decline                     | EEG +<br>PET SCAN +<br>None                           | Efficant of nlacma                            |      |
| receptor<br>enceptalitis catatonia rea<br>lupus erythematosus F 15 Acute stuporous MD<br>Lupus erythematosus F 15 Acute stuporous MD<br>catatonia rea<br>lupus erythematosus F 16 Acute stuporous MD<br>Other enceptalopathy F 16 Acute stuporous 00<br>Epileptic enceptalopathy F 9 Acute stuporous 00<br>Epileptic enceptalopathy F 14 Acute stuporous 00<br>Crictosnorin F 14 Ac | reatures<br>MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>Obsessive-   | Ptosts, myosts, epilepsy, ataxia<br>Post: frontal syndrome, memory<br>impairment<br>Medical history of LED<br>systemic manifestations<br>Medical history of LED  | antibodies: highly<br>+ in blood and CSF<br>Anaemia Coombs: +<br>Antibodies: + (antinuclear,<br>anti DNA, antinucleosome,<br>anticardiolipin, anti SSA,<br>SM, ribosomal P)<br>Anaemia, neutropenia,<br>antibodies: +<br>(antinucleosome,<br>anticardiolipin anti-RNP,<br>anti Sm), complement decline   | PEI SCAN +<br>None                                    | ΕΠΙταιγ νι μιασιτία                           | 6    |
| Lupus erythematosus       F       15       Acute stuporous       ME         Lupus erythematosus       F       16       Acute stuporous       ME         Cupus erythematosus       F       16       Acute stuporous       ME         Epileptic encephalopathis       F       9       Acute stuporous       Ob         Epileptic encephalopathy       F       14       Acute stuporous       Ob         Iatrogenic encephalopathy       F       14       Acute stuporous       Ob         (ciclosnorin)       Catatonia       Acute stuporous       Ob  | MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>Obsessive-   | Medical history of LED<br>Medical history of LED<br>systemic manifestations<br>Medical history of LED  | Anaemia Coombs: +<br>Antibodies: + (antinuclear,<br>anti DNA, antinucleosome,<br>anticardiolipin, anti SSA,<br>SM, ribosomal P)<br>Anaemia, neutropenia,<br>antibodies: +<br>(antinucleosome,<br>anticardiolipin anti-RNP,<br>anti Sm), complement decline   | None  | exchange and<br>Immunosunnressive             |      |
| Lupus erythematosus     F     15     Acute stuporous     ME       Lupus erythematosus     F     15     Acute stuporous     ME       Lupus erythematosus     F     15     Acute stuporous     ME       Lupus erythematosus     F     16     Acute stuporous     ME       Cupus erythematosus     F     16     Acute stuporous     ME       Lupus erythematosus     F     16     Acute stuporous     ME       Epileptic encephalopathies     P     Acute stuporous     Ob       Epileptic encephalopathy     F     9     Acute stuporous     Ob       Idrogenic encephalopathy     F     14     Acute stuporous     ME       (ricksnorin)     Catatonia     Correstionia     Acute stuporous     Ob   | MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>Obsessive-   | Medical history of LED<br>Impaired general health, multi<br>systemic manifestations<br>Medical history of LED  | Anaemia Coombs: +<br>Antibodies: + (antinuclear,<br>anti DNA, antinucleosome,<br>anticardiolipin, anti SSA,<br>SM, ribosomal P)<br>SM, ribosomal P)<br>Anaemia, neutropenia,<br>antibodies: +<br>(antinucleosome,<br>anti Sm), complement decline  | None  | therapy                                       |      |
| Catatonia       fea         Lupus erythematosus       F       15       Acute stuporous       ME         Lupus erythematosus       F       16       Acute stuporous       ME         Lupus erythematosus       F       16       Acute stuporous       ME         Culter ercephalopathies       F       16       Acute stuporous       ME         Epileptic encephalopathy       F       9       Acute stuporous       Ob         Iatrogenic encephalopathy       F       14       Acute stuporous       MC   | features<br>MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>Obsessive-<br>compulsive and   | Impaired general health, multi<br>systemic manifestations<br>Medical history of LED  | Antibodies: + (antinuclear,<br>anti DNA, antinucleosome,<br>anticardiolipin, anti SSA,<br>SM, ribosomal P)<br>Anaemia, neutropenia,<br>antibodies: +<br>(antinucleosome,<br>anticardiolipin anti-RNP,<br>anti Sm), complement decline  |   | Efficacy of plasma                            | 8    |
| Lupus erythematosus     F     15     Acute stuporous     MD       Lupus erythematosus     F     16     Acute stuporous     MD       Dther encephalopathies     P     Acute stuporous     Ob       Epileptic encephalopathy     F     9     Acute stuporous     Ob       Iatrogenic encephalopathy     F     14     Acute stuporous     MD       (ciclosnorin)     Catatonia     and     and   | MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>Obsessive-<br>compulsive and   | Impaired general health, multi<br>systemic manifestations<br>Medical history of LED  | ant DNA, antuncteosonic,<br>anticardiolipin, anti SSA,<br>Anæmia, neutropenia,<br>antibodies: +<br>(antinucleosome,<br>anticardiolipin anti-RNP,<br>anti Sm), complement decline   |   | exchange and                                  |      |
| Lupus erythematosus     F     15     Acute stuporous     ME       Lupus erythematosus     F     16     Acute stuporous     ME       Lupus erythematosus     F     16     Acute stuporous     ME       Other encephalopathies     F     9     Acute stuporous     Obs       Epileptic encephalopathy     F     9     Acute stuporous     Obs       Iatrogenic encephalopathy     F     14     Acute stuporous     ME   | MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>Obsessive-<br>compulsive and   | Impaired general health, multi<br>systemic manifestations<br>Medical history of LED  | SM, ribosomal P)<br>Anaemia, neutropenia,<br>antibodies: +<br>(antinucleosome,<br>anticardiolipin anti-RNP,<br>anti Sm), complement decline  |   | therapy                                       |      |
| Lupus erythematosus     F     15     Acute stuporous     MD       Lupus erythematosus     F     16     Acute stuporous     MD       Lupus erythematosus     F     16     Acute stuporous     MD       Other encephalopathy     F     9     Acute stuporous     Ob       Epileptic encephalopathy     F     9     Acute stuporous     Ob       Iatrogenic encephalopathy     F     14     Acute stuporous     MD       (richosnorin)     catatonia     ann     ann   | MDE with psychotic<br>features<br>MDE with psychotic<br>features<br>Obsessive-<br>compulsive and   | Impaired general health, multi<br>systemic manifestations<br>Medical history of LED  | Anaemia, neutropenia,<br>antibodies: +<br>(antinucleosome,<br>anticardiolipin anti-RNP,<br>anti Sm), complement decline  |   |   |      |
| catatonia fea<br>Lupus erythematosus F 16 Acute stuporous ME<br>catatonia fea<br>Other encephalopathies 5 Acute stuporous Ob<br>Epileptic encephalopathy F 9 Acute stuporous Ob<br>Iatrogenic encephalopathy F 14 Acute stuporous ME<br>(richosnorin) catatonia and   | features<br>MDE with psychotic<br>features<br>Obsessive-<br>compulsive and   | systemic manifestations<br>Medical history of LED  | antibodies: +<br>(antinucleosome,<br>anticardiolipin anti-RNP,<br>anti Sm), complement decline   | MRI +   | Efficacy of plasma exchange                   | 10   |
| Lupus erythematosus     F     16     Acute stuporous     ME       Catatonia     fea       Other encephalopathics     9     Acute stuporous     Ob       Epileptic encephalopathy     F     9     Acute stuporous     Ob       Iatrogenic encephalopathy     F     14     Acute stuporous     ME       (richosnorin)     catatonia     any   | MDE with psychotic<br>features<br>Obsessive-<br>compulsive and   | Medical history of LED   | (antunucteosonie,<br>anticardiolipin anti-RNP,<br>anti Sm), complement decline   | Scintigraphy +  | and Immunosuppressive                         |      |
| Lupus erythematosus     F     16     Acute stuporous     ME       Catatonia     fea       Other encephalopathies     9     Acute stuporous     Ob       Epileptic encephalopathy     F     9     Acute stuporous     Ob       Iatrogenic encephalopathy     F     14     Acute stuporous     ME       (richosnorin)     catatonia     any   | MDE with psychotic<br>features<br>Obsessive-<br>compulsive and   | Medical history of LED   | anti Sm), complement decline   | - EEG +   | шетару  |      |
| Lupus erythematosus     F     16     Acute stuporous     ML       Other encephalopathies     catatonia     fea       Dileptic encephalopathy     F     9     Acute stuporous     Ob       Epileptic encephalopathy     F     9     Acute stuporous     Ob       Iatrogenic encephalopathy     F     14     Acute stuporous     ML       (richosnorin)     catatonia     any   | MDE with psychotic<br>features<br>Obsessive-<br>compulsive and   | Medical history of LED   |  |   |   |      |
| catatonia fea<br>Other encephalopathies<br>Epileptic encephalopathy F 9 Acute stuporous Ob<br>catatonia an<br>latrogenic encephalopathy F 14 Acute stuporous MC<br>(richsnorin) catatonia and   | features<br>Obsessive-<br>compulsive and   | cincton human  | Antinuclear antibodies +   | MRI +   | Efficacy of plasma exchange                   | 10   |
| Other encephalopathies<br>Epileptic encephalopathy F 9 Acute stuporous Ob-<br>catatonia an<br>any<br>latrogenic encephalopathy F 14 Acute stuporous MC<br>(richsnorin) and  | Obsessive-<br>compulsive and   | circatonid modera  |  | EEG +   | and Immunosuppressive                         |      |
| Other encephalopathies<br>Epileptic encephalopathy F 9 Acute stuporous Ob<br>catatonia cor<br>latrogenic encephalopathy F 14 Acute stuporous MD<br>(richosnorin) catatonia and  | Obsessive-<br>compulsive and   | Cinctum transformed  |  | Scintigraphy +  | therapy                                       |      |
| Epileptic encephalopathy         F         9         Acute stuporous         Ob.           catatonia         catatonia         cor         any           latrogenic encephalopathy         F         14         Acute stuporous         ML           (richosnorin)         catatonia         any         any  | Obsessive-<br>compulsive and   | Entland, hundratio   |  |   |   |      |
| cortatonia cort<br>any<br>latrogenic encephalopathy F 14 Acute stuporous ML<br>(richosnorin) and  | compulsive and   | Epilepsy, ilypoloilla,   | None   | EEG +   | Efficacy of antiepileptic                     | 80   |
| latrogenic encephalopathy F 14 Acute stuporous MIC<br>(richosnorin) carlatonia and  |  | cognitive regression,<br>wyramidal cyndrome  |  |   | medication                                    |      |
| (ciclosporin) catatonia and   | MDE with psychotic   | Temporal spatial disorientation.   | None   | MRI +   | lmprovement after                             | ~    |
|   | and melancholic features   | cognitive impairment   |  | EEG +   | stopping ciclosporin                          | )    |
| Post insuline F 16 Acute stuporous MD   | MDE with   | Temporality, cognitive   | None   | EEG +   | None  | 5    |
| coma encephalopathy catatonia me  | melancholic features   | impairment, disorientation   |  |   |   |      |
| Genetic and metabolic conditions  |  |  |  |   |   |      |
| Intracerebral M 17 Acute stuporous Sch  | Schizophrenia  | Frontal and extrapyramidal   | 5HT deficit in the CSF   | EEG +   | None  | 5    |
| serotonin deficit catatonia   |  | syndrome, headache, facial paralysis,  |  |   |   |      |
|   |  | cerebellum syndrome,<br>tremor extranyramidal syndrome   |  |   |   |      |
| Storage disease M 16 Progressive Sch  | Schizophrenia  | Episode 1:   | Further explorations   | Abdominal ultrasound:                                 | None  | 9    |
| excited catatonia   |  | splenomegalia, confusion   | refused by parents   | hepatomegaly, splenomegaly                            |   |      |
|   |  | Episode 2 during   | Niemann Pick disease   |   |   |      |
|   |  | tollow-up: dysarthria, frontal<br>sions sunra nuclear naralvsis  | ruled out after skin biopsy  |   |   |      |
| Huntington's disease M 16 Progressive psychomotor Sch   | or Schizophrenia   | Family history of Huntington's   | Patient who knew   | IRM abnormalities                                     | None  | ~    |
| automatism  |  | disease with molecular diagnosis   | his mother diagnosis refused   | in basal ganglia                                      |   |      |
| Chorea (unknown origin) M 15 Progressive stuporous Sch  | Schizo-affective   | Choreiform movements appeared  | Molecular testing underway   |   | None  | 5    |
| catatonia dis   | disorder   | during follow-up under clozapine   | (Huntington ruled out)   |   |   |      |
| ProDH mutation M 14 Acute excited catatonia Sch   | Schizophrenia  | Parental history   | PRODH gene mutation +  |   | None  | 7    |
|   |  | of schizophrenia   | Moderate hyperprolinemia   |   |   |      |
| Fatal Familial Insomnia M 18 Acute non ML   | MDE with   | Insomnia, dysautonomia,  | PNRP D178N/129   | Polysomnography +,                                    | Worse with BZD                                | 6    |
| malignant catatonia psy   | psychotic symptoms   | dysarthria, ataxia, myoclonus  | Mutation +   | EEG +   | and ECT                                       |      |

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A. Consoli et al. / Schizophrenia Research 137 (2012) 151-158

155

### A. Consoli et al. / Schizophrenia Research 137 (2012) 151-158

#### Table 3

Variables associated with organic or developmental history in children and adolescent with catatonia.

|                           | Organic condition (N=13) | Developmental history (N=16) | Others (N=29) | Р     |  |  |
|---------------------------|--------------------------|------------------------------|---------------|-------|--|--|
| Psychiatric diagnosis     | N (%)                    |                              |               |       |  |  |
| Schizophrenia             | 30.8                     | 81.2                         | 58.6          | 0.025 |  |  |
| EDM                       | 46.2                     | 18.8                         | 31            | 0.29  |  |  |
| Mania                     | 15.4                     | 0                            | 13.8          | 0.244 |  |  |
| PDD                       | 0                        | 75                           | 0             | _     |  |  |
| MR                        | 0                        | 50                           | 0             | _     |  |  |
| Brief psychotic           | 7.7                      | 0                            | 6.9           | 0.59  |  |  |
| episode                   |                          |                              |               |       |  |  |
| Onset of catatonia N      | (%)                      |                              |               |       |  |  |
| Sudden                    | 76.9                     | 25                           | 65.5          | 0.008 |  |  |
| Insidious                 | 33.1                     | 75                           | 34.5          |       |  |  |
|                           |                          |                              |               |       |  |  |
| Type of catatonia N (%)   |                          |                              |               |       |  |  |
| Acute                     | 83.3                     | 43.8                         | 72.4          | 0.066 |  |  |
| Chronic                   | 16.7                     | 56.2                         | 27.6          |       |  |  |
| Cit                       | ( ( ( ) )                |                              |               |       |  |  |
| Severity scales mean      | $(\pm SD)$               | <u> </u>                     | с <b>г</b>    | 0.2   |  |  |
| CGI admission             | 0.0                      | 0.9                          | 0.0           | 0.3   |  |  |
| CGI discharge             | 4.4                      | 4.5                          | 4.0           | 0.46  |  |  |
| GAF admission             | 19.6                     | 16.9                         | 19.6          | 0.41  |  |  |
| GAF discharge             | 50.6                     | 44.2                         | 55.5          | 0.06  |  |  |
| Bush–Francis catatonia RS |                          |                              |               |       |  |  |
| Catalensy                 | 09                       | 19                           | 16            | Ns    |  |  |
| Stupor                    | 2.0                      | 1.5                          | 1.5           | Ns    |  |  |
| Posturing                 | 1.5                      | 1.1                          | 1.7           | Ns    |  |  |
| Waxy flexibility          | 0.9                      | 07                           | 0.8           | Ns    |  |  |
| Staring                   | 21                       | 13                           | 15            | Ns    |  |  |
| Negativism                | 19                       | 2.5                          | 1.8           | Ns    |  |  |
| Stereotypes               | 0.7                      | 14                           | 0.7           | Ns    |  |  |
| Psychomotor               | 0.5                      | 0.9                          | 0.8           | Ns    |  |  |
| excitement                | 0.5                      | 0.5                          | 0.0           | 145   |  |  |
| Automatic<br>movements    | 0.4                      | 1.6                          | 1.0           | 0.02  |  |  |
| Muscular rigidity         | 1.1                      | 0.7                          | 1.1           | Ns    |  |  |
| Social withdrawal         | 2.3                      | 2.3                          | 2.5           | Ns    |  |  |
| Mutism                    | 16                       | 14                           | 1.8           | Ns    |  |  |
| Mannerism                 | 0.2                      | 0.9                          | 0.4           | Ns    |  |  |
| Echopraxy                 | 0.1                      | 0.5                          | _             | 0.012 |  |  |
| Echolaly                  | 0.2                      | 0.6                          | 02            | Ns    |  |  |
| Incontinence              | 13                       | 0.8                          | 0.8           | Ns    |  |  |
| Verbigeration             | 0.9                      | 0.7                          | 0.5           | Ns    |  |  |
| Schizophasia              | 03                       | -                            | 0.1           | Ns    |  |  |
| Acrocyanosis              | _                        | 04                           | 03            | Ns    |  |  |
| Refusal to eat            | 16                       | 13                           | 1.5           | Ns    |  |  |
| Total score               | 20.2                     | 22.3                         | 20.2          | Ns    |  |  |
| I UTUI JUUIU              | 6-1 3 f = 6-1            |                              | 6-11-6-       |       |  |  |

following an insulin overdose suicide attempt in the context of a major depressive episode. Because this patient's CAUS score was equal to 5, we cannot exclude the possibility that catatonia was due to the depressive episode. We included this patient in the medical condition group because catatonia continued from the hypoglycaemic coma. Furthermore, catatonia had parallel EEG symptoms of brain suffering, including: generally asymmetrical background activity slowed to 6 Hz observed in posterior regions; weak reactivity to opening and closing of eyes; discrete fast beta rhythms (in microvolts), predominately in anterior regions; frequent bursts of delta waves; and acute right temporo-occipital and left temporal activity. Hyperpnoea increased these abnormalities.

Regarding the genetic risk factors associated with catatonia, we found one patient with Huntington's disease. This result is not surprising because: (i) this disease includes basal ganglia dysfunction (Walker, 2007), which has been implicated in the physiopathology of catatonia (Northoff, 2002), and (ii) early-onset Huntington's disease is associated with schizophrenia (Ribai et al., 2007; van Duijn et al., 2008). Similarly, both storage disease (Sedel et al., 2007) and FFI are associated with psychosis in the early stages of the disease

(Zeidler et al., 1997). For patients with PRODH mutations, the lack of a parental assessment prevented a homozygosity diagnosis. However, the association between schizophrenia and PRODH (Jacquet et al., 2002), and the association between schizophrenia and the 22q11 region, where the PRODH gene is located, are well documented (Green et al., 1992). Future research should explore whether a COMT polymorphism contributed to this patient's physiopathology (de Chaldee et al., 1999). Finally, the CAUS score was only 5 in 2 patients, meaning that we could only assess a possible relationship with catatonia. One patient exhibited chorea during the follow-up visit. We ruled out autoimmune chorea and Huntington's disease but genetic exploration is ongoing. The other patient had a 5HTP-CSF deficiency. Serotonin CSF deficit is a rare condition that was only described recently. In the largest study conducted with children who have neuropsychiatric conditions, this deficit was associated with various syndromes including inborn error of metabolism (e.g., mitochondrial disorder), pontocerebellar hypoplasia, Rett syndrome, epileptic encephalopathies, leucodystrophies and neuropsychiatric disturbances (e.g., autism spectrum disorder and severe behavioural problems) (De Grandis et al., 2010). Our genetic investigation is ongoing, but the TPH2 (tryptophane hydroxylase-2) gene sequencing was negative (data not shown). A serotonin deficit may not explain the patient's entire clinical presentation, but the possibility is interesting enough to be mentioned.

### 4.2. Clinical implications

The results presented here have several implications regarding changes in the diagnosis of catatonia in DSM-V. First, our data (consistent with previous reports, (Dhossche et al., 2010)) emphasise the importance of searching for a medical condition in young people with catatonia. Second, consistent with findings in adults (Taylor and Fink, 2003), our results support the view that catatonia in youth is a relatively homogeneous clinical syndrome, with a heterogeneous set of associated psychiatric and medical disorders that require extensive diagnostic evaluation. Clinical and socio-demographic features were quite similar in patients with different psychiatric and medical diagnoses, with only a few exceptions: insidious onset, echopraxia and automatic compulsive movements were more frequent in patients with a developmental disorder, but these are known features of PDD, the diagnosis in 75% of these cases; and schizophrenia was significantly less frequent in patients with a medical condition, but 38% did have a schizophrenia diagnosis, and thus no psychiatric diagnosis was uniquely associated with any of our three subgroups. Thus, catatonia is rather homogeneous as a clinical syndrome, regardless of the underlying medical, psychiatric, or developmental conditions.

These results are relevant to the debate over the fate of catatonia in DSM-V (Francis et al., 2010). Catatonia patients are best served when the syndrome is rapidly recognised, specific syndromal treatment is provided (such as benzodiazepines) and consideration is given to appropriate (and often aggressive) medical work-up, with continuity of care to ensure that the work-up is completed even after discharge from hospital care. The first proposal of the DSM-V workgroup (June 2010) to delete the codes 295.2 (Schizophrenia, Catatonic type) and 293.89 (Catatonia secondary to a medical condition), and to make catatonia a "specifier" added as a fifth digit to several other diagnoses (some of the psychotic disorders and all of the mood and bipolar disorders) seems likely to reduce rather than enhance clinician awareness of all of these points, particularly during psychiatric training.

By contrast, a large group of experts advocated a unique and broadly-defined code for catatonia as a syndrome, which can be diagnosed acutely in addition to any suspected or established associated disorders (Francis et al., 2010). Integrating this view to the debate, the DSM-V workgroup reconsidered (January 2011) the proposal and recommends now to maintain the category "Catatonia secondary

156

#### A. Consoli et al. / Schizophrenia Research 137 (2012) 151-158

to a medical condition" and to add a new category "Catatonia not otherwise specified" (298.99) (www.dsm5.org). Our results support this last proposal. Catatonia is a treatable condition when properly recognised. Symptomatic treatments include high doses of benzodiazepine (Taylor and Fink, 2003), ECT, or both (Consoli et al., 2010). When available, complementary treatments of comorbid medical conditions are warranted (e.g., patients with auto-immune catatonia) (Consoli et al., 2011; Marra et al., 2008). The first step, however, is recognising catatonia. Establishing a distinct, broad diagnostic entity of catatonia syndrome seems most likely to promote optimal clinical care.

#### 4.3. Limitations and strengths

The results of the current study should be interpreted in the context of its limitations. (i) The low prevalence of catatonia in youths explains the sample size of this study (N = 58) (Cohen et al., 2005; Takaoka and Takata, 2003; Thakur et al., 2003). (ii) Because we were not blind to the participant diagnoses, we cannot be certain that our search for associated medical condition in patients with BP was as accurate as patients with catatonia; however, both types of patients were at the same hospital and followed up in average for 8 years (Cohen et al., 2009; Louet et al., 2010). (iii) The lack of a paediatric department at Salpêtrière Hospital might explain the absence of infectious disease in this study; similarly, the brief acute catatonic states that can occur in adolescents with substance abuse problems are usually treated in emergency care (Masi et al., 2002; Maxwell et al., 1993). (iv) Possible recruitment biases regarding patients with catatonia as we received more patients after 2006 (see methods). However, there was no increase of medical conditions after 2006 (8(20%) vs. 5(27%), respectively, p = 0.51). The strengths of this study include (i) the large amount of data and the prospective design, (ii) the recruitment of participants over a 17-year period, (iii) the length of hospitalisation during which patients were assessed and treated, (iv) the fact that this sample is the largest in the literature, and (v) the comparison of patients with catatonia to patients with severe BP.

## 5. Conclusion

Catatonia in children and adolescents is associated with a high prevalence of medical conditions. This needs to be acknowledged as it may greatly delay the treatment of catatonia and the diagnosis of medically related catatonia. Tragically, this may deny patients' treatment opportunities.

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#### **Conflict of interest**

Dr. Bonnot reported receiving travel support from Actelion; Dr. Cohen reported past consultation for or the receipt of honoraria from Schering-Plough, Bristol-Myers Squibb, Otsuka, Janssen, and Sanofi-Aventis; Dr. Consoli reported receiving travel support from Bristol-Myers Squibb; Drs. Amoura, Bodeau, Campion, Laurent, An-Gourfinkel, and Sedel have no relationship that might have interest in the submitted work; their spouses, partners or children have no financial relationship that may be relevant to the submitted work; all authors have no non-financial interests that may be relevant to the submitted work.

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#### References

- Begaud, B., Evreux, J.C., Jouglard, J., Lagier, G., 1985. Imputation of the unexpected or toxic effects of drugs. Actualization of the method used in France. Therapie 40 (2), 111–118.
- Bender, H.U., Almashanu, S., Steel, G., Hu, C.A., Lin, W.W., Willis, A., Pulver, A., Valle, D., 2005. Functional consequences of PRODH missense mutations. Am. J. Hum. Genet. 76 (3), 409–420.
- Breakey, W.R., Kala, A.K., 1977. Typhoid catatonia responsive to ECT. Br. Med. J. 2 (6083), 357–359.
- Brunelle, J., Consoli, A., Tanguy, M.L., Huynh, C., Perisse, D., Deniau, E., Guile, J.M., Gerardin, P., Cohen, D., 2009. Phenomenology, socio-demographic factors and outcome upon discharge of manic and mixed episodes in hospitalized adolescents: a chart review. Eur. Child Adolesc. Psychiatry 18 (3), 185–193.
- Bush, G., Fink, M., Petrides, G., Dowling, F., Francis, A., 1996. Catatonia. I. Rating scale and standardized examination. Acta Psychiatr. Scand. 93 (2), 129–136.
- Cohen, D., Flament, M., Dubos, P.F., Basquin, M., 1999. Case series: catatonic syndrome in young people. J. Am. Acad. Child Adolesc. Psychiatry 38 (8), 1040–1046.
- Cohen, D., Nicolas, J.D., Flament, M.F., Perisse, D., Dubos, P.F., Bonnot, O., Speranza, M., Graindorge, C., Tordjman, S., Mazet, P., 2005. Clinical relevance of chronic catatonic schizophrenia in children and adolescents: evidence from a prospective naturalistic study. Schizophr. Res. 76 (2–3), 301–308.
- Cohen, D., Guile, J.M., Brunelle, J., Bodeau, N., Louet, E., Lucanto, R., Consoli, A., 2009. Bipolar episodes in adolescents: diagnostic issues and follow-up in adulthood. Encéphale 35 (Suppl. 6), S224–S230.
- Consoli, A., Benmiloud, M., Wachtel, L., Dhossche, D., Cohen, D., Bonnot, O., 2010. Electroconvulsive therapy in adolescents with the catatonia syndrome: efficacy and ethics. J. ECT 26 (4), 259–265.
- Consoli, A., Ronen, K., An-Gourfinkel, I., Barbeau, M., Marra, D., Costedoat-Chalumeau, N., Montefiore, D., Maksud, P., Bonnot, O., Didelot, A., Amoura, Z., Vidailhet, M., Cohen, D., 2011. Malignant catatonia due to anti-NMDA-receptor encephalitis in a 17-year-old girl: case report. Child Adolesc. Psychiatr. Ment. Health 5 (1), 15.
- Cornic, F., Consoli, A., Cohen, D., 2007. Catatonia in children and adolescents. Psychiatr. Ann. 37, 19–26.
- Cornic, F., Consoli, A., Tanguy, M.L., Bonnot, O., Perisse, D., Tordjman, S., Laurent, C., Cohen, D., 2009. Association of adolescent catatonia with increased mortality and morbidity: evidence from a prospective follow-up study. Schizophr. Res. 113 (2–3), 233–240.
- Cottencin, O., Warembourg, F., de Chouly de Lenclave, M.B., Lucas, B., Vaiva, G., Goudemand, M., Thomas, P., 2007. Catatonia and consultation-liaison psychiatry study of 12 cases. Prog. Neuropsychopharmacol. Biol. Psychiatry 31 (6), 1170–1176.
- Dalmau, J., Bataller, L., 2007. Limbic encephalitis: the new cell membrane antigens and a proposal of clinical-immunological classification with therapeutic implications. Neurologia 22 (8), 526–537.
- Dalmau, J., Gleichman, A.J., Hughes, E.G., Rossi, J.E., Peng, X., Lai, M., Dessain, S.K., Rosenfeld, M.R., Balice-Gordon, R., Lynch, D.R., 2008. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 7 (12), 1091–1098 (Dec, Epub 2008 Oct 11).
- Dalmau, J., Lancaster, E., Martinez-Hernandez, E., Rosenfeld, M.R., Balice-Gordon, R., 2011. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 10 (1), 63–74.
- de Chaldee, M., Laurent, C., Thibaut, F., Martinez, M., Samolyk, D., Petit, M., Campion, D., Mallet, J., 1999. Linkage disequilibrium on the COMT gene in French schizophrenics and controls. Am. J. Med. Genet. 88 (5), 452–457.
   De Grandis, E., Serrano, M., Perez-Duenas, B., Ormazabal, A., Montero, R., Veneselli, E.,
- De Grandis, E., Serrano, M., Perez-Duenas, B., Ormazabal, A., Montero, R., Veneselli, E., Pineda, M., Gonzalez, V., Sanmarti, F., Fons, C., Sans, A., Cormand, B., Puelles, L., Alonso, A., Campistol, J., Artuch, R., Garcia-Cazorla, A., 2010. Cerebrospinal fluid alterations of the serotonin product, 5-hydroxyindolacetic acid, in neurological disorders. J Inherit Metab Dis 33 (6), 803–809.
- Dhossche, D., Wing, L., Ohta, M., Neümarker, K.J., 2006. Catatonia in autism spectrum disorders. Int. Rev. Neurobiol. 72.
- Dhossche, D., Cohen, D., Ghaziuddin, N., Wilson, C., Wachtel, L.E., 2010. The study of pediatric catatonia supports a home of its own for catatonia in DSM-5. Med. Hypotheses 75 (6), 558–560.

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#### A. Consoli et al. / Schizophrenia Research 137 (2012) 151-158

- Dimitri, D., Jehel, L., Durr, A., Levy-Soussan, M., Andreux, V., Laplanche, J.L., Fossati, P., Cohen, D., 2006. Fatal familial insomnia presenting as psychosis in an 18-yearold man. Neurology 67 (2), 363-364.
- Elia, J., Dell, M.L., Friedman, D.F., Zimmerman, R.A., Balamuth, N., Ahmed, A.A., Pati, S., 2005. PANDAS with catatonia: a case report. Therapeutic response to lorazepam and plasmapheresis. J. Am. Acad. Child Adolesc. Psychiatry 44 (11), 1145-1150.

Endicott, J., Spitzer, R., Fleiss, J., 1976. GAF (Global Assessment of Functioning Scale).

Ev. H., 1950. Etudes Psychiatriques. Desclée de Brouwer and cie. Paris.

- Florance, N.R., Davis, R.L., Lam, C., Szperka, C., Zhou, L., Ahmad, S., Campen, C.J., Moss, H., Peter, N., Gleichman, A.J., Glaser, C.A., Lynch, D.R., Rosenfeld, M.R., Dalmau, J., 2009. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann. Neurol. 66 (1), 11-18.
- Francis, A., Fink, M., Appiani, F., Bertelsen, A., Bolwig, T.G., Braunig, P., Caroff, S.N., Carroll, B.T., Cavanna, A.E., Cohen, D., Cottencin, O., Cuesta, M.J., Daniels, J., Dhossche, D., Fricchione, G.L., Gazdag, G., Ghaziuddin, N., Healy, D., Klein, D., Kruger, S., Lee, J.W., Mann, S.C., Mazurek, M., McLall, W.Y., McDaniel, W.W., Northoff, G., Peralta, V., Petrides, G., Rosebush, P., Rummans, T.A., Shorter, E., Suzuki, K., Thomas, P., Vaiva, G., Wachtel, L., 2010. Catatonia in Diagnostic and Statistical Manual of Mental Disorders, fifth edition. J. ECT 26 (4), 246-247.
- Green, W.H., Padron-Gayol, M., Hardesty, A.S., Bassiri, M., 1992. Schizophrenia with childhood onset: a phenomenological study of 38 cases. J. Am. Acad. Child Adolesc. Psychiatry 31 (5), 968-976.
- Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology. National Institute of Mental Health, Bethesda, New York.
- Jacquet, H., Raux, G., Thibaut, F., Hecketsweiler, B., Houy, E., Demilly, C., Haouzir, S., Allio, G., Fouldrin, G., Drouin, V., Bou, J., Petit, M., Campion, D., Frebourg, T., 2002. PRODH mutations and hyperprolinemia in a subset of schizophrenic patients. Hum. Mol. Genet. 11 (19), 2243-2249.
- Lahutte, B., Cornic, F., Bonnot, O., Consoli, A., An-Gourfinkel, I., Amoura, Z., Sedel, F., Cohen, D., 2008. Multidisciplinary approach of organic catatonia in children and adolescents may improve treatment decision making. Prog. Neuropsychopharmacol. Biol. Psychiatry 32 (6), 1393-1398.
- Lanham, J.G., Brown, M.M., Hughes, G.R., 1985. Cerebral systemic lupus erythematosus presenting with catatonia. Postgrad. Med. J. 61 (714), 329–330.
  Lee, A., Glick, D.B., Dinwiddie, S.H., 2006. Electroconvulsive therapy in a pediatric pa-
- tient with malignant catatonia and paraneoplastic limbic encephalitis. J. ECT 22 (4), 267–270.
- Lord, C., Rutter, M., Le Couteur, A., 1994. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J. Autism Dev. Disord. 24 (5), 659–685. Louet, E., Consoli, A., Lucanto, R., Duplant, N., Bailly-Salin, M.J., Lemoigne, A., Martin, M.,
- Mayer, C., Thompson, C., Gollier-Briant, F., Laurent, C., Brunelle, J., Bodeau, N., Cohen, D., 2010. Psychodynamic-oriented psychological assessment predicts evolution to schizophrenia at 8-year follow-up in adolescents hospitalized for a manic/mixed episode: interest of an overall subjective rating. J. Physiol. Paris 104 (5), 257-262.
- Marra, D., Amoura, Z., Soussan, N., Haroche, J., Consoli, A., Ghillami-Dalbin, P., Diemert, M.C., Musset, L., Piette, J.C., Cohen, D., 2008. Plasma exchange in patients with stuporous catatonia and systemic lupus erythematosus. Psychother. Psychosom. 77 (3), 195-196.
- Masi, G., Mucci, M., Floriani, C., 2002. Acute catatonia after a single dose of ecstasy. J. Am. Acad. Child Adolesc. Psychiatry 41 (8), 892. Maxwell, D.L., Polkey, M.I., Henry, J.A., 1993. Hyponatraemia and catatonic stupor after
- taking "ecstasy". BMJ 307 (6916), 1399.

- Naranjo, C.A., Busto, U., Sellers, E.M., Sandor, P., Ruiz, I., Roberts, E.A., Janecek, E., Domecq, C., Greenblatt, D.J., 1981. A method for estimating the probability of ad-verse drug reactions. Clin. Pharmacol. Ther. 30 (2), 239–245.
- Northoff, G., 2002. What catatonia can tell us about "top-down modulation": a neuropsychiatric hypothesis. Behav. Brain Sci. 25 (5), 555-577 (discussion 578-604).
- Nurnberger Jr., J.I., Blehar, M.C., Kaufmann, C.A., York-Cooler, C., Simpson, S.G., Harkavy-Friedman, J., Severe, J.B., Malaspina, D., Reich, T., 1994. Diagnostic Interview for Genetic Studies. Rationale, unique features, and training. NIMH genetics initiative. Arch. Gen. Psychiatry 51 (11), 849-859 (discussion 863-844).
- Perisse, D., Amoura, Z., Cohen, D., Saintigny, P., Mekhloufi, F., Mazet, P., Piette, J.C., 2003. Case study: effectiveness of plasma exchange in an adolescent with systemic lupus erythematosus and catatonia. J. Am. Acad. Child Adolesc. Psychiatry 42 (4), 497-499
- Primavera, A., Fonti, A., Novello, P., Roccatagliata, G., Cocito, L., 1994. Epileptic seizures in patients with acute catatonic syndrome. J. Neurol. Neurosurg. Psychiatry 57 (11), 1419-1422.
- Ribai, P., Nguyen, K., Hahn-Barma, V., Gourfinkel-An, I., Vidailhet, M., Legout, A., Dode, C., Brice, A., Durr, A., 2007. Psychiatric and cognitive difficulties as indicators of juvenile Huntington disease onset in 29 patients. Arch. Neurol. 64 (6), 813-819.
- Schimmel, M., Bien, C.G., Vincent, A., Schenk, W., Penzien, J., 2009. Successful treatment of anti-N-methyl-D-aspartate receptor encephalitis presenting with catatonia. Arch. Dis. Child. 94 (4), 314-316.
- Sedel, F., Baumann, N., Turpin, J.C., Lyon-Caen, O., Saudubray, J.M., Cohen, D., 2007. Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. J. Inherit. Metab. Dis. 30 (5), 631-641.
- Taieb, O., Flament, M.F., Chevret, S., Jeammet, P., Allilaire, J.F., Mazet, P., Cohen, D., 2002. Clinical relevance of electroconvulsive therapy (ECT) in adolescents with severe mood disorder: evidence from a follow-up study. Eur. Psychiatry 17 (4), 206–212.
- Takaoka, K., Takata, T., 2003. Catatonia in childhood and adolescence. Psychiatry Clin. Neurosci. 57 (2), 129-137.
- Taque, S., Peudenier, S., Gie, S., Rambeau, M., Gandemer, V., Bridoux, L., Betremieux, P., De Parscau, L., Le Gall, E., 2004. Central neurotoxicity of cyclosporine in two children with nephrotic syndrome, Pediatr, Nephrol, 19 (3), 276-280.
- Taylor, M.A., Fink, M., 2003. Catatonia in psychiatric classification: a home of its own. Am. J. Psychiatry 160 (7), 1233-1241.
- Thakur, A., Jagadheesan, K., Dutta, S., Sinha, V.K., 2003. Incidence of catatonia in children and adolescents in a paediatric psychiatric clinic. Aust. N. Z. J. Psychiatry 37 (2), 200-203.
- Unni, K.E., Shivakumar, V., Dutta, T.K., Chandrasekaran, R., 1995. Fever of unknown cause presenting as catatonia. J. Assoc. Physicians India 43 (2), 134–135. van Duijn, E., Kingma, E.M., Timman, R., Zitman, F.G., Tibben, A., Roos, R.A., van der
- Mast, R.C., 2008. Cross-sectional study on prevalences of psychiatric disorders in mutation carriers of Huntington's disease compared with mutation-negative first-degree relatives. J. Clin. Psychiatry 69 (11), 1804-1810.
- Wachtel, L.E., Kahng, S., Dhossche, D.M., Cascella, N., Reti, I.M., 2008. ECT for catatonia in an autistic girl. Am. J. Psychiatry 165 (3), 329–333.
- Walker, F.O., 2007. Huntington's disease. Lancet 369 (9557), 218-228.
- Wing, L., Shah, A., 2000. Catatonia in autistic spectrum disorders. Br. J. Psychiatry 176, 357-362.
- Zeidler, M., Johnstone, E.C., Bamber, R.W., Dickens, C.M., Fisher, C.J., Francis, A.F., Goldbeck, R., Higgo, R., Johnson-Sabine, E.C., Lodge, G.J., McGarry, P., Mitchell, S., Tarlo, L., Turner, M., Ryley, P., Will, R.G., 1997. New variant Creutzfeldt–Jakob disease: psychiatric features. Lancet 350 (9082), 908-910.

158