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Psychiatric autoimmune conditions in children and adolescents: Is catatonia a severity marker?

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ABSTRACT

Objectives: Patients with autoimmune encephalitis (AE) are likely to exhibit an acute onset of severe psychiatric features, including psychosis and/or catatonia. Based on the high prevalence of catatonia in AE and our clinical experience, we hypothesized that catatonia might be a marker of severity requiring more aggressive treatment approaches.

Methods: To reach a sufficient number of cases with brain-autoimmune conditions, we pooled two samples (N = 58): the first from the French National Network of Rare Psychiatric diseases and the second from the largest Italian neuro-pediatrics center for encephalopathies. Autoimmune conditions were diagnosed using a multidisciplinary approach and numerous paraclinical investigations. We retrospectively compared patients with and without catatonia for psychiatric and non-psychiatric clinical features, biological and imaging assessments, type of immunotherapy used and outcomes.

Results: The sample included 25 patients (43%) with catatonia and 33 (57%) without catatonia. Forty-two patients (72.4%) had a definite AE (including 27 anti-NMDA receptor encephalitis) and 16 (27.6%) suspected autoimmune encephalitis. Patients with catatonia showed significantly more psychotic features [18 (72%) vs 9 (27.3%), $p < 0.001$)] and more movement disorders [25 (100%) vs 20 (60.6%), $p < 0.001$] than patients without catatonia. First line (corticoids, immunoglobulin and plasma exchanges) and second line (e.g., rituximab) therapies were more effective in patients with catatonia, with 24 (96%) vs 22 (66.7%) ($p = 0.006$) and 17 (68%) vs 9 (27.3%) ($p = 0.002$), respectively. However, those with catatonia received more combinations of first and second line treatments and had more relapses during outcomes.

Conclusion: Despite its exploratory design, the study supports the idea that autoimmune catatonia may be a marker of severity and morbidity in terms of initial presentation and relapses, requiring the need for early and aggressive treatment.

Abbreviations: ASD, autism spectrum disorders; AE, autoimmune encephalitis; CAUS, causality assessment score; CNV, copy number variation; CSF, cerebral spinal fluid; CNS, central nervous system; ECT, electro-convulsive therapy; EEG, electroencephalogram; EOS, early onset schizophrenia; FDG PET, 18F-Flurodeoxyglucose positron emission tomography; HE, Hashimoto encephalopathy; TPO, thyroperoxidase; TG, thyroglobulin; ID, intellectual disability; IgG, immunoglobulin G; MRI, magnetic Resonance Imaging; OCD, obsessive compulsive disorder; PANS, Pediatric Acute-onset Neuropsychiatric Syndrome; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcus infections; PCRS, Pediatric Catatonia Rating Scale; PE, plasma exchange; SLE, systemic lupus erythematosus

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1. Introduction

Pediatric catatonia is a rare and severe psychomotor syndrome associated with a large variety of psychiatric (early onset schizophrenia (EOS); autism spectrum disorder (ASD) and intellectual disability (ID)) (Cohen et al., 2005; Cohen, 2006; Dhossche, 2014; Withane and Dhossche, 2019; Ghaziuddin et al., 2015; Fink et al., 2006) and non-psychiatric conditions and with high rates of mortality and morbidity (Cornic et al., 2009). The prevalence of pediatric catatonia in the hospital setting is estimated at between 0.6% and 17.7%. Symptomatic treatment consists initially of high dosage benzodiazepines (e.g.; lorazepam) (Raffin et al., 2015). In the case of resistance or life-threatening conditions; electro-convulsive therapy (ECT) is effective and safe in youth (Dhossche, 2014; Raffin et al., 2015; Puffer et al., 2016; Consoli et al., 2010). Approximately 20% of catatonias are secondary to an underlying medical condition, including genetic, neurological, infectious and autoimmune disorders (Consoli et al., 2012; Raffin et al., 2018). Therefore, specific etiological treatments can lead to catatonia improvement (Consoli et al., 2012; Ferrafiat et al., 2016; Ferrafiat et al., 2018; Lahutte et al., 2008; Marra et al., 2008) and have crucial impact on the prognosis (Ferrafiat et al., 2018; Byrne et al., 2015; Finke et al., 2012; Florance et al., 2009; Dale et al., 2017; Hacohen et al., 2013). Autoimmune disorders, such as anti-NMDA receptor encephalitis (Florance et al., 2009; Titulaer et al., 2013), Systemic Lupus Erythematosus (SLE) (Tucker et al., 2008; Hoffman et al., 2009; Livingston et al., 2011), Hashimoto Encephalopathy (HE) (Montagna et al., 2016; Mahmud et al., 2003; Carlone et al., 2013) and Pediatric Autoimmune Disorders Associated with Streptococcus infections (PANDAS)/Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) (Swedo et al., 2015; Elia et al., 2005; Schlansky et al., 2019), are likely to exhibit an acute onset of severe psychiatric features at an early stage, including catatonia. The association between catatonia and severe psychiatric features (hallucinations, delusions, mood disorders and cognitive regression) remains rare and atypical in youths and is to be considered as a red flag for possible underlying autoimmune disorders. The identification of well characterized antibodies in plasma or cerebral spinal fluid (CSF) can be challenging, as a substantial proportion of youth with suspected autoimmune encephalitis is seronegative (Dale et al., 2017; Hacohen et al., 2013; Lee et al., 2016). Those conditions require the early introduction of aggressive immunosuppressive treatment to limit neurological and cognitive sequelae (Byrne et al., 2015; Florance et al., 2009; Titulaer et al., 2013). Moreover, autoimmune catatonia seems to respond well to the early introduction of plasma exchange (Ferrafiat et al., 2016; Ferrafiat et al., 2018; Marra et al., 2008). Despite potential adverse effects (e.g., infections, malignancies, infertility) (Titulaer et al., 2013; Kashyape et al., 2012), the risk–benefit ratio for using immunosuppressive treatment in youth remains favorable due to high mortality and morbidity rates (Byrne et al., 2015; Titulaer et al., 2013; Zekeridou et al., 2015).

To date, there are few data regarding catatonia in autoimmune conditions. Most of the studies about autoimmune systemic disorders and autoimmune encephalitis have focused on neurological aspects, such as epilepsy and movement disorders and autonomic dysfunction, even though catatonia is considered as a movement disorder by some authors (Granata et al., 2018; Graus et al., 2016). Psychiatric features in autoimmune conditions that are common have been broadly assessed. Assessments have mainly detailed psychotic and mood symptoms in the adult population. However, catatonia has often been reported in patients with autoimmune conditions, in particular in anti-NMDA encephalitis and lupus. One study proposed a subtype of catatonic anti-NMDA encephalitis (DeSena et al., 2014). Our previous study underlined the key role of catatonia as a red flag for different types of autoimmune conditions (Ferrafiat et al., 2018).

Here, we aimed to explore whether pediatric patients with autoimmune encephalitis exhibiting catatonia differed from patients with autoimmune encephalitis that did not. To do so, we retrospectively compared the following factors among a large series of patients with autoimmune encephalitis: 1) psychiatric and non-psychiatric clinical features and paraclinical characteristics; and 2) the clinical outcomes in terms of response to treatment, relapses, sequelae and death between patients with and without catatonia. Based on the high prevalence of catatonia in autoimmune disorders, our clinical experience with autoimmune catatonia (Consoli et al., 2012; Ferrafiat et al., 2016; Ferrafiat et al., 2018; Lahutte et al., 2008; Marra et al., 2008), and on a study suggesting a predominant catatonic subtype of anti-NMDA receptor encephalitis with poorer treatment response (DeSena et al., 2014), we hypothesized that catatonia might be a marker of severity in terms of initial clinical presentation and outcomes, with a higher risk of resistance to treatment for autoimmune conditions.

2. Methods

2.1. Participants

This publication involves current clinical practice and is based on a clinical study in compliance with the Ethics of the University Centers. The study was conducted and approved according to the hospital ethics committee's regulations. The French sample included every child and adolescent inpatient admitted for a severe acute psychiatric presentation (catatonia, acute psychosis episode, cognitive regression, hallucinations, and mood disorders) and a diagnosis of autoimmune conditions from 4 departments of Child and Adolescent Psychiatry belonging to a National network for rare psychiatric diseases: i) University Hospital La Pitié-Salpêtrière, Paris, France between 1993 and 2017; ii) University Hospital Charles Nicolle, Rouen, France between 2013 and 2017; iii) University Hospital of Lille, France between 2015 and 2017; iv) University Hospital of Angers, France between 2015 and 2017. The Italian sample included every child and adolescent inpatient admitted for suspicion of acute encephalopathy to the Department of Pediatric Neuroscience at the Foundation IRCCS Neurological Institute "Carlo Besta", Milan, Italy between 2010 and 2017.

2.2. Inclusion criteria

Patients had to fulfill two main criteria:

1. Showing an autoimmune condition that included: autoimmune systemic disorders (SLE, Hashimoto encephalopathy, PANDAS) and autoimmune encephalitis. Autoimmune encephalitis (AE) was divided into two types: definite AE with the existence of well-known CSF antibodies (anti-NMDA, anti-GAD, anti-Hu) and suspected AE. The suspected AE criteria included the previously described "possible AE" and "probable AE" according to the criteria proposed by Graus et al (Graus et al., 2016). However, a substantial proportion of children with suspected AE was seronegative with negative MRI and normal CSF testing and therefore did not fulfill the current criteria for possible or probable AE proposed by Graus et al. (Dale et al., 2017; Hacohen et al., 2013). Hence, we proposed that patients with suspected AE must fulfill the following criteria: i) rapid progression (less than 3 months) of working memory deficits, altered mental status, or severe psychiatric symptoms; ii) at least one of the following: new focal central nervous system (CNS) findings, seizures not explained by previous seizure disorder, CSF pleiocytosis, and MRI or 18F-Flurodeoxyglucose positron emission tomography (FDG

PET) features suggestive of encephalitis. Giving recent data supporting that FDG PET could be more sensitive than conventional imaging for the detection of AE (Morbelli et al., 2016; Probasco et al., 2017; Turpin et al., 2019), we purposely added PET scan features to the previous possible AE criteria from Graus et al.; iii) therapeutic challenge with immunosuppressive or immunomodulatory treatments was positive; iv) reasonable exclusion of alternative causes. To help define when a medical condition could be causal in pediatric catatonia (Consoli et al., 2012), we also retrospectively used a causality assessment score (CAUS). In autoimmune and pediatric setting, CAUS helps diagnose autoimmune conditions even in the absence of formal identification of autoantibodies with a validated threshold score ≥ 5, allowing early and aggressive use of immunosuppressive treatment (Ferrafiat et al., 2018).

2. Patients should present acute severe neuropsychiatric symptoms, including a systematic assessment of catatonia. In addition to catatonia, the main psychiatric presentations included: an acute psychotic episode; mood disorders, such as manic, mixed or depressive episodes with or without psychotic features; severe cognitive regression (global or specific) and isolated hallucinations (visual, auditory). In the French network, the diagnosis of catatonia was made when patients presented at least two motor symptoms or one motor and one non-motor symptom (Mutism, Negativism, Echolalia, Verbigeration, Withdrawal, Incontinence, Schizophasia, Acrocyanosis, Autonomic abnormality) indicative of severe behavioral and emotional impairment. The catatonic symptom list was based on a validated modified version of the Bush and Francis scale: the Pediatric Catatonia Rating Scale (PCRS) (Benarous et al., 2016). In the Italian center, catatonia was systematically searched using DSM5 criteria. They included the presence of three symptoms from the following list of twelve signs: stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerisms, stereotypy, agitation, grimacing, echolalia, and echopraxia.

2.3. Patient assessment

For each patient, each center systematically and retrospectively assessed: i) socio-demographic data (sex, age); ii) autoimmune and psychiatric history; iii) the type of autoimmune condition: autoimmune systemic disorders, definite AE and suspected AE; iv) the presence and type of catatonia, the presence and type of psychotic features (hallucinations, delusions), the presence of mood disorders (manic, depressive symptoms), ASD features, obsessive compulsive disorder (OCD), anxiety features, sleep disorders, and cognitive regression. Regarding the neurological signs, we systematically reported any movement disorders and seizures. All possible systemic localizations, such as cutaneous, digestive, or rheumatologic expression, were also systematically searched.

To maximize the accuracy of medical diagnoses, we used previously proposed guidelines for clinical and paraclinical investigations to help determine the medical conditions associated with catatonia and/or acute psychotic episodes (Cornic et al., 2009; Ferrafiat et al., 2018; Lahutte et al., 2008; Sedel et al., 2007; Benarous et al., 2018). Neurological and global examinations were performed to identify medical conditions. Paraclinical investigations were performed accordingly to our previous published extensive panel when AE is suspected (Ferrafiat et al., 2018). Additional cerebral PET scanning was performed when the clinical presentation included fever and/or neurological signs and/or resistance to standard treatment and/or negative MRI. The use of PET scan in AE remains as a research topic and is not available in all pediatric settings (Morbelli et al., 2016). Some authors argue that FDG-PET imaging has low specificity regarding the cause of the disorder (Graus and Dalmau, 2016). However both Turpin et al. and Probasco et al. found a higher sensibility for PET compared to MRI, respectively in pediatric population (34 patients with AE, 94% PET abnormalities vs 41% MRI abnormalities) (Turpin et al., 2019) and adults (61 patients with AE, 85% PET abnormalities vs 68% MRI abnormalities) (Probasco et al., 2017). In our study, PET was considered abnormal based on local expert's interpretation. From the most recent literature data in adult and pediatric population, they usually consider the presence or absence of metabolism abnormalities mainly in cerebral cortex (Probasco et al., 2017; Turpin et al., 2019) and basal ganglia (Turpin et al., 2019) including: i) hypometabolisms in frontal and/or occipital lobes; ii) hypermetabolisms involving every five lobes; and iii) basal ganglia hypermetabolisms. All paraclinical data were retrospectively assessed by each center.

Due to the absence of treatment guidelines, each center had its own treatment algorithm. Etiological treatments were reviewed and systematically retrospectively classified into three groups: i) tumor removal; ii) first line treatments, including corticoids, intravenous immunoglobulins (IgG IV) and plasma exchanges (PE); and iii) second line treatments, including cyclophosphamide, mycophenolate mofetil, azathioprine, and rituximab. Despite differences in treatment algorithm, all centers ensured an early and timely introduction of both lines.

The response to treatment was clinically and retrospectively evaluated with a three-point scale based on the psychiatric and neurological clinical improvement evaluation by senior clinicians of each center: 0 for “no improvement,” when no improvement of either psychiatric or neurological symptoms was found; 1 for “partial improvement,” if at least one category of symptoms was improved; and 2 for “major improvement,” when both psychiatric and neurological symptoms were improved. In addition to treatment response, we also reported possible poor outcomes, such as relapse, sequelae and death. The outcome assessments were performed knowing if the patient was catatonic or not. Relapse was considered when the patient presented a similar or more severe clinical (psychiatric and neurological) presentation within the coming year following discharge. Sequelae had to occur after treatment response and included: i) persistent seizures and/or movement disorders; ii) cognitive impairment, such as memory loss, language deficit, attention deficit, or persistence of the initial cognitive regression; and iii) persistent chronic psychiatric features requiring the long-term use of standard psychiatric treatment (e.g., antipsychotic, mood stabilizer, and antidepressant). The follow up period available for all patients was at least one year after treatment introduction.

2.4. Statistical analysis

This is a retrospective analysis of pooled data from 5 centers. We compared patients with catatonia versus patients without catatonia for categorical variables: sex; autoimmune conditions; subtypes of catatonia (stuporous and/or agitated); psychiatric features; neurological symptoms with movement disorders and seizures; systemic localization; plasma biological arguments; CSF biological arguments; abnormal EEG; abnormal MRI; abnormal PET scan; type of treatment used with tumor removal, first line and second line treatments; treatment response to first and/or second line treatments with the categories of “partial” and “major” improvement combined as “positive response” for binary percentages of improvement ; relapses; sequelae and death. The quantitative variables compared between the two groups included age and CAUS score.

Quantitative variables were described using the means and standard deviation. Categorical variables were described using the numbers and percentages of occurrences. Quantitative variables were compared using either Welch's t-test or Wilcoxon rank-sum test depending on the graphically assessed normality assumption. Categorical variables were compared using either Chi-squared test or Fisher’s exact test if at least one expected count under the null hypothesis was less than five. Analyses were run using R software 3.4.0. A p-value less than 0.05 were considered significant. Given the sample size and lack of statistical correction, this study is only exploratory.

3. Results

3.1. Demographic and clinical characteristics

The French series included 23 patients: 14 patients had catatonia, and 9 did not. The Italian series comprised 35 patients: 11 patients had catatonia, and 24 did not. Fig. 1 summarizes the diagram flow of the study. In total, the sample included 58 patients with autoimmune neuropsychiatric conditions, 25 (43%) with catatonia and 33 (57%) without catatonia. The mean age was 13.86 (± 4.41) years. The majority of patients was females (66%). Participants' characteristics are given in Table 1. Among the catatonic group (N = 25), 15 (60%) exhibited a stuporous form, 6 (24%) an agitated form and 4 (16%) a mixed form. Forty-two patients (72.4%) were diagnosed with definite AE, including 27 anti-NMDA receptor encephalitis (46.55%), 5 SLE (8.62%), 2 anti-GAD encephalitis (3.45%), 2 anti-Hu encephalitis (3.45%), 2 Hashimoto encephalopathy (3.45%), 1 anti-VGKC/anti-LGI1 encephalitis (1.7%), 2 PANDAS/PANS (3.4%), and 1 SLE with anti-phospholipid-related chorea (1.7%). Suspected AE was identified for 16 patients (27.6%). The distribution of autoimmune conditions per site is listed in Table S1.

Regarding first line treatment, 42 patients received an initial therapeutic challenge with high dosage corticoid pulses, 35 patients (60%) received IgG IV, 11 (19%) had plasma exchanges (PE), 36 patients (62%) received at least two different first lines, and only one patient (1.7%) directly received second line treatment (rituximab) without previous first lines. The other 15 (26%) patients without high dosage corticoids received another first line: 10 had IgG IV alone, and 5 had PE alone. Second line treatments, including cyclophosphamide (8.6%), mycophenolate mofetil (5.2%), azathioprine (8.6%), and rituximab (29.2%), were indicated for 30 patients (52%) to maintain improvement after a positive response to first line treatment (high dosage corticoids and/or PE and/or IgG IV). Three patients (5%) underwent tumor removal besides immunomodulatory treatments. The participants' treatments are shown in Fig. 2

3.2. Clinical outcomes

First line therapies were effective (major or partial improvement) for 46 (79%) patients and not effective without any improvement for 12 (21%) patients. Second line therapies were effective, with major or partial improvement for 26 (87%), and 4 (13%) patients had no improvement. Seven patients (12%) relapsed. Fifteen (26%) patients exhibited sequelae within the one-year follow up, including: persistent seizures (N = 4), movement disorders (N = 0), cognitive impairment (N = 5, memory loss and language deficit), and chronic psychiatric features (N = 6, anxiety and mood disorders). Outcome data were not available for two patients. Only one catatonic patient (2%) died from complications of severe autonomic dysfunction due to anti-NMDA encephalitis.

Interestingly most patients with suspected AE exhibited catatonia (N = 10, 67%). Most of them fully responded to first lines including plasma exchange (N = 13, 81%). Only 3 of them (19%) required both first and second line. Half of them (N = 8) exhibited sequelae including cognitive impairment (N = 3) and chronic psychiatric features (N = 5, anxiety and mood disorders). Only one (6%) patient relapsed.

3.3. Patients with and without catatonia

Comparisons are given in Table 1. There were no differences between the two groups regarding sociodemographic data. A few differences emerged regarding clinical characteristics. Catatonic patients showed significantly more psychotic features than patients without catatonia (18 (72%) vs 9 (27.3%), p < 0.001), including more

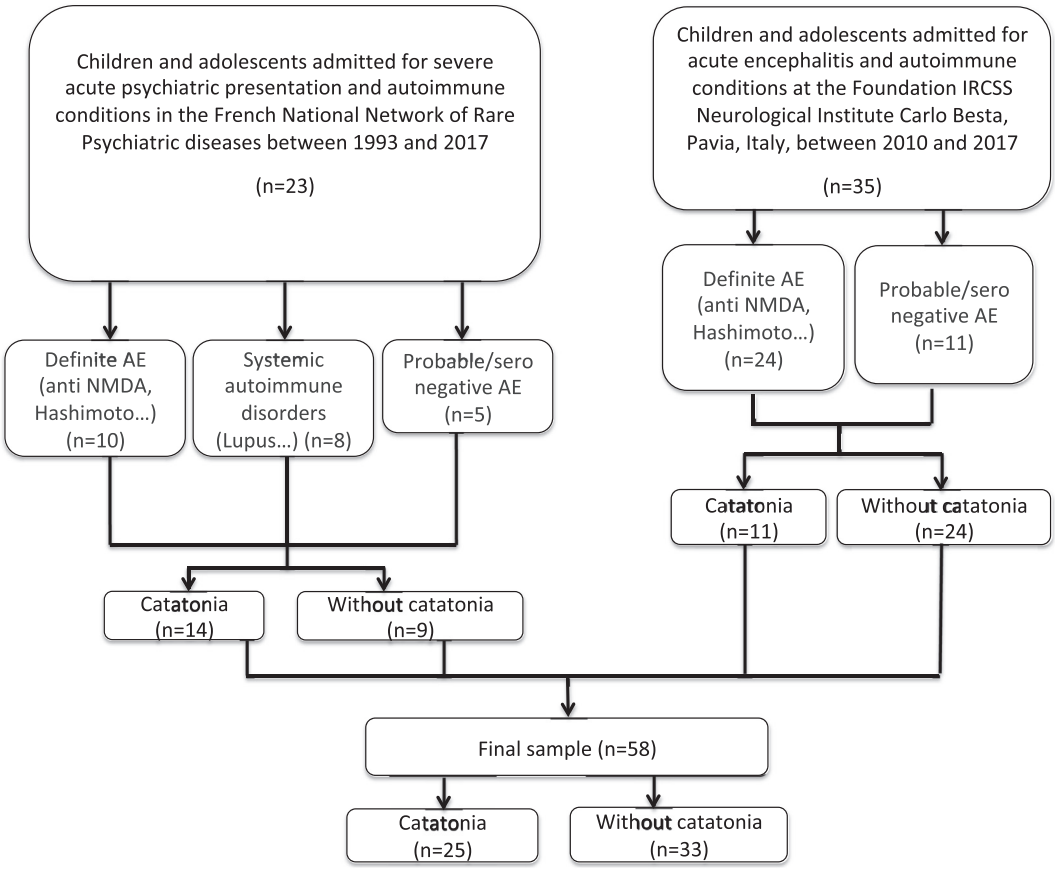

Fig. 1. Flow chart of the study. N: number, AE: autoimmune encephalitis.

Table 1
Socio-demographics and clinical characteristics of the patients with neuropsychiatric autoimmune conditions with and without catatonia.

	No catatonia (N = 33)	Catatonia (N = 25)	Total (N = 58)	P
	Socio-demographics			
Sex: N (%) females	20 (60.6%)	18 (72%)	38 (66%)	0.366^{WILCOXON}
Age: mean (SD)	13.39 (4.58)	14.48 (4.17)	13.86 (4.41)	0.243^{WILCOXON}
	Etiological classification			
CAUS score	7.42 (1.7)	7.56 (1.61)	7.47 (1.65)	0.731
Autoimmune systemic disorders: N (%)	3 (9.1%)	5 (20%)	8 (13.8%)	0.951
Definite AE: N (%)	21 (63.6%)	13 (52%)	34 (58.6%)	0.951
Suspected AE: N (%)	9 (27.3%)	7 (28%)	16 (27.6%)	0.951
	Clinical characteristics			
Stuporous catatonia: N (%)	0	19 (76%)	19 (33%)	< 0.001
Agitated catatonia: N (%)	0	10 (40%)	10 (17%)	< 0.001^{FISHER}
Hallucinations: N (%)	7 (21%)	17 (68%)	24 (41%)	< 0.001
Delusions: N (%)	6 (18.2%)	14 (56%)	20 (34%)	0.003
Psychotic symptoms: N (%)	9 (27.3%)	18 (72%)	27 (47%)	0.001
Mood disorders: N (%)	17 (51.5%)	19 (76%)	36 (62%)	0.057
ASD features: N (%)	0	4 (16%)	4 (7%)	0.03^{FISHER}
OCD: N (%)	2 (6.1%)	0	2 (3%)	0.501^{FISHER}
Anxiety features: N (%)	33 (100%)	20 (80%)	53 (91%)	0.012^{FISHER}
Sleep disorders: N (%)	19 (57.6%)	18 (72%)	37 (64%)	0.258
Cognitive regression: N (%)	19 (57.6%)	14 (56%)	33 (57%)	0.904
Movement disorders	20 (60.6%)	25 (100%)	45 (78%)	< 0.001
Seizures: N (%)	21 (63.6%)	12 (48%)	33 (57%)	0.234
Systemic localization: N (%)	7 (21.2%)	5 (20%)	12 (21%)	0.91
	Paraclinical characteristics			
Plasma biological arguments: N (%)	7 (21.2%)	6 (24%)	13 (22%)	0.801
CSF biological arguments: N (%)	24 (72.7%)	15 (60%)	39 (67%)	0.306
EEG arguments: N (%)	16 (48.5%)	15 (60%)	31 (53%)	0.384
MRI arguments: N (%)	15 (45.5%)	8 (33%)	23 (40%)	0.357
PET scan arguments: N (%)	1 (50%)	2 (66.7%)	3 (60%)	1^{FISHER}
	Treatment			
Tumor removal: N (%)	1 (3%)	2 (8%)	3 (5%)	0.572^{FISHER}
Corticoids: N (%)	25 (75.8%)	17 (68%)	42 (72%)	0.513
IgG IV: N (%)	23 (69.7%)	12 (48%)	35 (60%)	0.094
Plasma exchange: N (%)	4 (12 0.1%)	7 (28%)	11 (19%)	0.179^{FISHER}
Cyclophosphamide: N (%)	0	5 (20%)	5 (9%)	0.013^{FISHER}
Mycophemolate mofetil: N (%)	0	3 (12%)	3 (5%)	0.075^{FISHER}
Aziothropine: N (%)	2 (6.1%)	3 (12%)	5 (9%)	0.643^{FISHER}
Ritubimax: N (%)	7 (21.2%)	10 (40%)	17 (30%)	0.066
	Outcomes			
First line treatment efficacy: N (%)	22 (66.7%)	24 (96%)	46 (79%)	0.006
Second line treatment efficacy: N (%)	9 (27.3%)	17 (68%)	26 (45%)	0.002
Relapses: N (%)*	0	7 (29.2%)	7 (12%)	0.001^{FISHER}
Sequels: N (%)	8 (24%)	7 (28%)	15 (26%)	0.746
Death: N (%)	0	1 (4%)	1 (2%)	0.431^{FISHER}

AE: autoimmune encephalitis, ASD: autism spectrum disorder, OCD: obsessive–compulsive disorder, CSF: cerebro-spinal fluid; *N = 56; In most cases we used Chi2 tests for comparisons except when indicated.

delusional ideas and hallucinations. In addition, they had significantly more movement disorders (dystonia, choreiform or other non-specific abnormal movements): 25 (100%) vs 20 (60.6%), respectively, $p < 0.001$. In contrast, patients without catatonia had significantly more anxiety manifestations than catatonic ones, with 33 (100%) vs 5 (20%), respectively, $p = 0.012$.

Regarding the response to immunomodulatory or immunosuppressive treatment, first line (high dosage corticoids and/or PE and/or IgG IV) and second line (including cyclophosphamide, mycophenolate mofetil, and azathioprine, rituximab) therapies were found to be more effective for catatonic patients, with 24 (96%) versus 22 (66.7%) ($p = 0.006$) and 17 (68%) versus 9 (27.3%) ($p = 0.002$), respectively, showing a major or partial clinical response. However, they had more relapses than patients without catatonia, at 7 (29.2%) versus 0 (0%) ($p = 0.001$), respectively. No significant differences regarding sequelae or death were found between the two groups. Catatonic patients received all high dose benzodiazepines, and none received ECT.

4. Discussion

Few data exist regarding pediatric catatonia related to autoimmune conditions (Ferrafiat et al., 2016; Ferrafiat et al., 2016; Benarous et al., 2018; Mooneyham et al., 2018; Tanguturi et al., 2019). This study gathers one of the largest samples over several university hospitals, allowing a multi-disciplinary diagnosis and therapeutic approach through various pediatric departments. First, our study underscores that autoimmune catatonia is significantly more associated with severe psychotic features compared to autoimmune conditions without catatonia, suggesting a more severe initial psychiatric presentation. Second, our results stress that patients with catatonia experienced more relapses that patients without catatonia. These results emphasize that autoimmune catatonia could imply a more severe form of autoimmune condition, supporting our hypothesis. However, we did not find a higher risk of poorer outcomes in terms of treatment resistance, sequelae or death among catatonic patients. Given our results, we discuss four main points: i) catatonia in immune-related conditions; ii) treatment; iii) anti-NMDA receptor encephalitis, as we observed 27 cases; and iv) the limitations of our study.

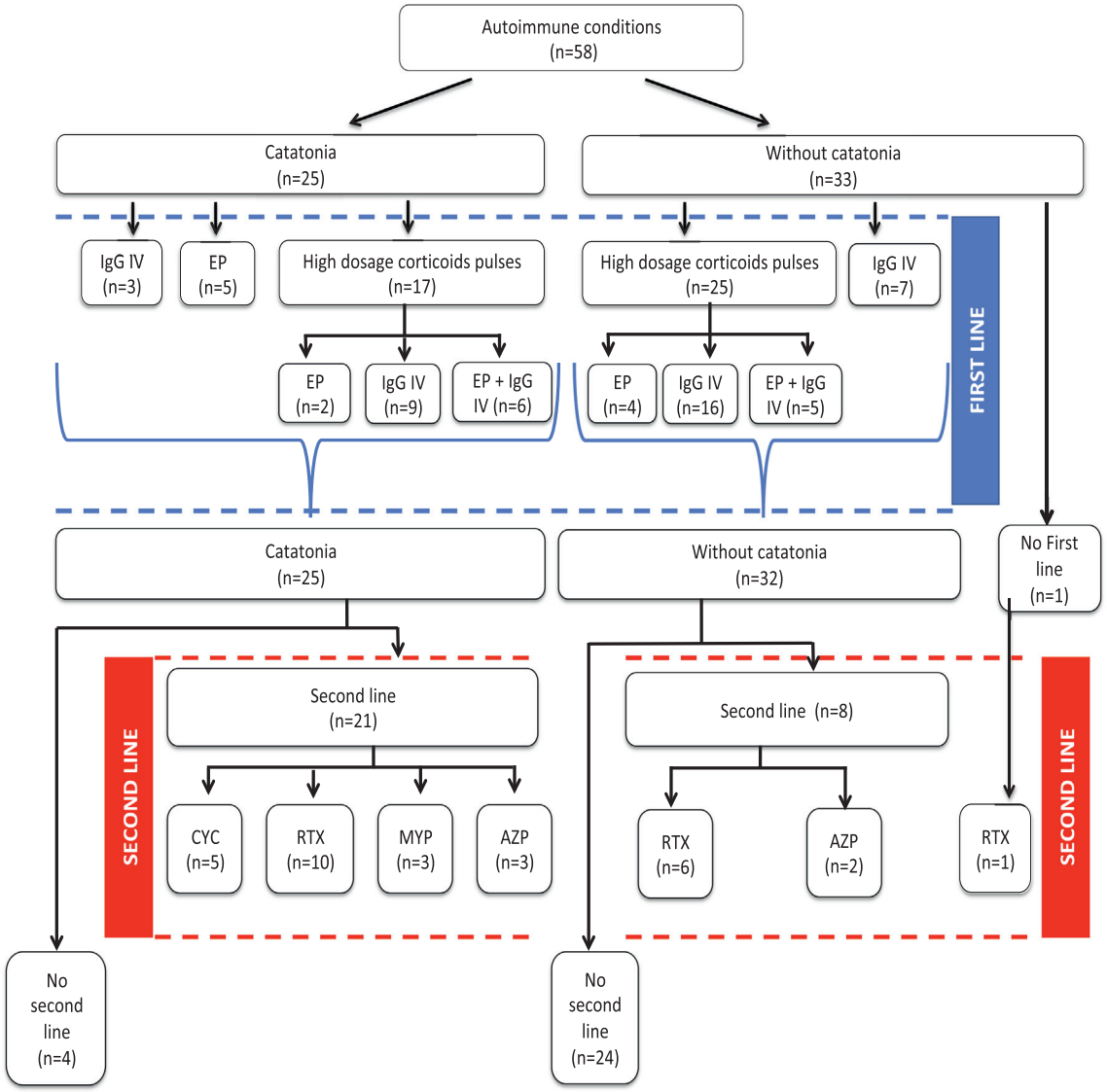

Fig. 2. Participants' first and second line treatments according to catatonia. IgG IV: intravenous immunoglobulins; PE: plasma exchange; CYC: cyclophosphamide; MYP: mycophenolate mofetil; AZP: azathioprine; RTX: rituximab.

Our results support the idea that catatonia is associated with more severe forms of autoimmune disorders, but we can generalize this finding outside the context of anti-NMDA receptor encephalitis, as half of our cases were secondary to another causal encephalitis. Catatonia was associated with more psychotic features, emphasizing the fact that autoimmune catatonia is likely to be associated with other severe psychiatric features, such as hallucinations, psychosis, cognitive regression, and fluctuation of symptoms, leading to an atypical psychiatric presentation in youths (Consoli et al., 2012; Ferrafiat et al., 2018; Bonnot et al., 2015). Regarding the significant difference in anxiety features between the two groups, the non-catatonic patients were more likely to express their anxiety and to be diagnosed, whereas catatonic patients presented difficulties in identifying and therefore expressing their inner subjective feelings and experiences during the acute phase (Cohen, 2006). Furthermore, catatonic patients had more relapses. Even if the prognosis of neurocognitive sequelae is related to the timing of the introduction of immunosuppressive treatment (Byrne et al., 2015; Florance et al., 2009; Titulaer et al., 2013; Armangue et al., 2012; Luca et al., 2011; Chapman and Vause, 2011; Nosadini et al., 2015), it is notable that catatonic patients were more severe with more relapses regardless of their initial positive response to first or second line therapies. Hypothetically, catatonia as a clinical marker of risk of relapse would require earlier (even presumptively) and more aggressive immunosuppressive treatment to better prevent relapses and neurocognitive sequelae. In contrast to DeSena et al., who hypothesized that anti-NMDA encephalitis with catatonia showed a poor response to immunosuppressive treatments (DeSena et al., 2014), our catatonic patients had a better response to either first or second line treatment than patients without catatonia. These results might be explained by two factors: i) our catatonic patients were clinically more severe and therefore had faster access to immunotherapy and more combinations of first and second line treatments (only 4 catatonic patients did not receive second line treatments compared to 24 without catatonia); ii) the lack of standardized international treatment guidelines makes it difficult to interpret our treatment data, as patients' treatment plans and access to immunosuppressive treatment were heterogeneous and widely differed from one center to another. To illustrate this heterogeneity, we found that immunoglobulin was often used in our Italian sample. Plasma exchanges were only available in 3 centers due to limited access to this procedure. Cyclophosphamide was mainly used in one center according to a published multidisciplinary treatment algorithm (Ferrafiat et al., 2018). The different treatments used in each

center are detailed in Fig. 2.

Regarding published data on treatment options, available studies suggest that the use of high dosage corticoids via pulses initially gives good response rates in pediatric populations (Armangue et al., 2012; Luca et al., 2011; Brunner et al., 2008; Levy and Kamphuis, 2012). However, plasma exchanges and their peripheral action represent an interesting option in SLE and anti-NMDA receptor encephalitis (Boers and Colebatch, 2001; DeSena et al., 2015; Hussain et al., 2005; Prytuła et al., 2015; Suppiej et al., 2016) and provide an effective treatment for catatonia (Ferrafiat et al., 2016; Marra et al., 2008; Elia et al., 2005). In the case of resistance to first line treatments (Armangue et al., 2012) or relapses, second line therapies are to be considered (Byrne et al., 2015; Florance et al., 2009; Dale et al., 2017; Titulaer et al., 2013; Stingl et al., 2018). The early introduction of second lines in youths ensure better outcomes (Luca et al., 2011; Stingl et al., 2018; Ishiura et al., 2008). For example, despite rituximab's significant risk of infectious complications, a recent study supports its early off-label use in youths with significant morbidity secondary to autoimmune disorders (Dale et al., 2014).

Regarding anti-NMDA receptor encephalitis, most studies are recent, and it is the most frequent form of AE. This was also the case in our sample, at nearly half of the cases, and 49% of those cases had catatonia. Movement disorders, such as stereotyped movements, dystonia, chorea and catatonia, are frequent and are considered to be key symptoms exhibited by patients (Granata et al., 2018; Dash et al., 2019; Duan et al., 2016; Dalmau et al., 2008). Graus et al. included rigidity and abnormal postures (that belong to catatonic features) among the movement disorders in new diagnosis criteria for anti-NMDA receptor encephalitis (Graus et al., 2016). Interestingly, two studies focusing on catatonia found that patients who had hypokinetic disorders, such as catatonia, took significantly longer to improve or did not fully recover compared to other forms of movement disorders (Granata et al., 2018; Dash et al., 2019). DeSena et al. proposed distinguishing 3 phenotypes of anti-NMDA receptor antibody encephalitis in children (DeSena et al., 2014): type 1 “classic anti-NMDA receptor antibody encephalitis with predominant movement disorder and epilepsy”; type 2 “psychiatric predominant NMDA receptor encephalitis subtype”; and type 3 “catatonia/stupor predominant anti-NMDA receptor encephalitis sub phenotype.” Type 3 patients were often very severe and showed the poorest response even to aggressive immunotherapies (DeSena et al., 2014). Anti-NMDA encephalitis emphasizes that our results cross paths with those previous available data in terms of severity, whether the severity is defined by the initial clinical presentation, treatment response, frequency of relapses or sequelae. Hence, our results extend the concept of catatonia as a marker of severity to autoimmune conditions in general.

However, the results should be interpreted in the context of several limitations. First, the number of subjects recruited was low, despite the multicentric recruitment. This could be explained by the very low prevalence of catatonia in youths compared to other psychiatric disorders (Cohen et al., 2005) and the low prevalence of autoimmune conditions among the pediatric population (Dale et al., 2017; Stingl et al., 2018). The statistical analysis should be regarded as exploratory. Second, to increase the number of patients with probable, suspected and definite AE, we grouped different samples that had recruitment biases, leading to heterogeneity. Indeed, 60% of the cases came from the Italian autoimmune encephalitis specialized center, with a lower proportion of catatonia compared to the French network specialized in pediatric catatonia. Additionally, the two centers had a different first-step inclusion criterion, highlighting center-based biases. As a consequence, generalization may not be valid. Third, we used a multicenter clinical sample of acutely ill patients recruited in university teaching hospitals that may have been particularly enriched for subjects with more severe forms of neuropsychiatric autoimmune conditions.

5. Conclusion

Despite its exploratory nature, this study enhances the need to consider catatonia as a marker of possible underlying autoimmune conditions, as many children and adolescents with suspected autoimmune encephalitis are seronegative (Dale et al., 2017). It also underscores the idea that catatonia can be a marker of severity and morbidity in terms of associated psychiatric symptoms and outcomes. Finally, the response of autoimmune catatonia to treatment, along with a higher relapse rate further supports the existing literature for both early and aggressive immunosuppressive treatments.

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Ethical Statement

This publication involves current clinical practice and is based on a clinical study in compliance with the Ethics of the University Centers. All the parents were informed of the possible further use of clinical, paraclinical and treatment data regarding their child and gave their consent for use of those data in the context of research.

CRediT authorship contribution statement

Vladimir Ferrafiat: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Visualization. **Elise Riquin:** Methodology, Investigation, Data curation, Writing - original draft. **Elena Freri:** Methodology, Investigation, Data curation, Writing - original draft. **Tiziana Granata:** Writing - review & editing. **Nardo Nardocci:** Writing - review & editing. **François Medjkane:** Writing - review & editing. **Claire Corfiotti:** Writing - review & editing. **Alessandra Tozzo:** . **Huges Pellerin:** Formal analysis, Writing - original draft. **Xavier Benarous:** Writing - review & editing. **Julien Haroche:** Writing - review & editing. **Zahir Amoura:** Writing - review & editing. **Philippe Duverger:** Writing - review & editing. **Renaud Jardri:** Writing - review & editing. **Priscille Gerardin:** Writing - review & editing. **David Cohen:** Conceptualization, Methodology, Investigation, Data curation, Writing - review & editing, Visualization. **Angèle Consoli:** Writing - review & editing. **Marie Raffin:** Conceptualization, Methodology, Investigation, Data curation, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2020.110028.

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