Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

A causality algorithm to guide diagnosis and treatment of catatonia due to autoimmune conditions in children and adolescents

Vladimir Ferrafiat [a,d,*], Marie Raffin [a], Elena Freri [b], Tiziana Granata [b], Nardo Nardocci [b], Federica Zibordi [b], Nicolas Bodeau [a], Xavier Benarous [a], Bertrand Olliac [a], Elise Riquin [e], Jean Xavier [a], Sylvie Viaux [a], Julien Haroche [c], Zahir Amoura [c], Priscille Gerardin [d], David Cohen [a,f], Angèle Consoli [a,g]

[a] Department of Child and Adolescent Psychiatry, Université Pierre et Marie Curie, Hôpital Pitié-Salpêtrière, AP-HP, 47-83 Boulevard de l'Hôpital, 75013 Paris, France
[b] Department of Pediatric Neuroscience, Foundation I.R.C.C.S. Neurological Institute "C. Besta", Via Celoria 11, 20133 Milan, Italy
[c] French National Reference Center for Rare Systemic AutoImmune Disorders, E3M Institute, Université Pierre et Marie Curie, Hôpital Pitié-Salpêtrière, AP-HP, 47-83 Boulevard de l'Hôpital, 75013 Paris, France
[d] Department of Child and Adolescent Psychiatry, Université de Rouen, Hôpital Charles Nicolle, 1 rue de Germont, 76000 Rouen, France
[e] Pediatric Psychiatry Department, Hôpital Universitaire d'Angers, 4 Rue Larrey, 49100 Angers, France
[f] CNRS UMR 7222, Institut des Systèmes Intelligents et Robotiques, Université Pierre et Marie Curie, Hôpital Pitié-Salpêtrière, AP-HP, 47-83 Boulevard de l'Hôpital, 75013 Paris, France
[g] Groupe de Recherche Clinique, Abord dimensionnel des épisodes psychotiques de l'enfant et de l'adolescent: implications génétiques, métaboliques et auto-immunes, Université Pierre et Marie Curie, Hôpital Pitié-Salpêtrière, AP-HP, 47-83 Boulevard de l'Hôpital, 75013 Paris, France

ARTICLE INFO

Article history:
Received 3 April 2017
Received in revised form 16 June 2017
Accepted 20 June 2017
Available online xxxx

Keywords:
Catatonia
Autoimmune condition
Immunosuppressive treatment
Encephalitis

ABSTRACT

Objectives: Pediatric catatonia is a rare and life-threatening syndrome. Around 20% of juvenile catatonia is associated with organic condition (Consoli et al., 2012). Autoimmune conditions represent a diagnostic and therapeutic challenge since specific antibodies can be missed. To facilitate decision making, we recently formulated a causality assessment score (CAUS) using a stepwise approach and an immunosuppressive therapeutic challenge (Ferrafiat et al., 2016). Our objectives were to validate retrospectively CAUS and to define its threshold for an accurate distinction between organic catatonia and non-organic catatonia, and specifically between autoimmune catatonia and non-organic catatonia.
Method: To obtain a sufficient number of cases with organic catatonia, we pooled two samples ($N = 104$) – one from a child psychiatry center, the other from neuro-pediatrics center – expert in catatonia and autoimmune conditions. Organic conditions were diagnosed using a multidisciplinary approach and numerous paraclinical investigations. Given the binary classification needs, we used receiver operating characteristic (ROC) analysis (Peacock and Peacock, 2010) to calculate the best classification threshold.
Results: The cohort included 67 cases of non-organic catatonia and 37 cases of organic catatonia. ROC analysis showed that the CAUS performance in discriminating both organic catatonia vs. non-organic catatonia, and autoimmune catatonia vs. non-organic catatonia was excellent (Area Under the Curve = 0.99). In both analyses, for a CAUS threshold ≥ 5, accuracy equaled to 0.96.
Conclusion: Regarding juvenile catatonia, the use of the CAUS score algorithm combining a therapeutic challenge and a threshold ≥ 5 may help to diagnose and treat autoimmune conditions even without formal identification of auto-antibodies.

1. Introduction

Catatonia is a severe syndrome gathering motor and psychic symptoms that may result in death (Dimitri et al., 2006). Numerous medical conditions and severe psychiatric conditions such as schizophrenia and mood disorder can exhibit catatonia. Catatonia in psychiatry inpatient setting is rare although one study from India reported higher rates (Cohen et al., 2005; Thakur et al., 2003). Mortality and morbidity rates are higher in catatonic patients than in any other psychiatric conditions (Cornic et al., 2009). Symptomatic treatment consists in high dosage benzodiazepines (e.g., lorazepam) at first (Raffin et al., 2015). In case of resistance or life-threatening condition, electro-convulsive therapy (ECT) is effective and safe in youth (Consoli et al., 2010; Dhossche, 2014; Puffer et al., 2016; Raffin et al., 2015). However etiological treatment remains the specific treatment for organic catatonia.

Catatonia seems to be "organic" in nature with important physiological and biological changes. Besides medical complications of catatonia,

* Corresponding author at: Department of Child and Adolescent Psychiatry, Université Pierre et Marie Curie, Hôpital Pitié-Salpêtrière, AP-HP, 47-83, boulevard de l'Hôpital, 75013 Paris, France.
E-mail address: Vladimir.Ferrafiat@chu-rouen.fr (V. Ferrafiat).

http://dx.doi.org/10.1016/j.schres.2017.06.036
0920-9964/

we distinguish catatonia with and without a medical condition with contributive factors (medical/neurological/immune findings) for a causal relationship. This occurrence is labeled "organic catatonia" in this manuscript. Up to 20% of pediatric catatonias are secondary to a medical condition such as neurometabolic disorders or genetic conditions (Lahutte et al., 2008). Therefore, specific treatments targeting causal organic conditions can lead to catatonia improvement (Consoli et al., 2012; Ferrafiat et al., 2016; Lahutte et al., 2008; Marra et al., 2008) and have crucial impact on the prognosis (Byrne et al., 2015; Ferrafiat et al., 2016; Finke et al., 2012). Autoimmune disorders take an important role as an underlying condition to catatonia (Ferrafiat et al., 2016). Pediatric cases with catatonia have been described in systemic lupus erythematosus (SLE) (Marra et al., 2008), pediatric autoimmune neuropsychiatric disorders associated with streptococcus infections (PANDAS) (Elia et al., 2005) and anti-NMDA receptor encephalitis (Florance et al., 2009). Their treatment represents a challenge since it implies the early use of immunosuppressive therapies as the neurological and cognitive prognosis appears to be time related to their introduction (Byrne et al., 2015; Florance et al., 2009; Titulaer et al., 2013). Despite potential adverse effects (e.g., infections, malignancies, infertility and premature gonadal failure) (Kashyape et al., 2012; Titulaer et al., 2013), the risk-benefit ratio for the use of immunosuppressive drugs in youth remains favorable due to high mortality and morbidity rates (Byrne et al., 2015; Titulaer et al., 2013; Zekeridou et al., 2015). Autoimmune conditions also represent a diagnostic and therapeutic challenge since specific and contributive antibodies can be missed despite systematic and repetitive search (Hacohen et al., 2013). Diagnostic criteria available for autoimmune encephalitis rely on antibody testing and response to immunotherapy (Zuliani et al., 2012). Besides antibody testing is not easily accessible in many institutions, results can take several weeks to obtain, and the absence of autoantibodies does not exclude the possibility that a disorder is immune mediated (Hacohen et al., 2013). Hence, the concept of levels of clinical evidence for autoimmune encephalitis has been proposed. Instead of the usual dichotomy (autoimmune vs. non autoimmune), it proposes to distinguish possible, probable and definite autoimmune encephalitis (Graus et al., 2016). Criteria to classify the probability of encephalitis include: i) conventional clinical neurological assessment: subacute onset of working memory deficits, altered mental status, or psychiatric symptoms; ii) standard diagnostic tests (Magnetic Resonance Imaging (MRI), electroencephalogram (EEG), and cerebral spinal fluid (CSF) studies); and iii) reasonable exclusion of alternative causes.

Following the same principle of level of clinical evidence in the context of pediatric catatonia (Consoli et al., 2012; Ferrafiat et al., 2016) we published a causality assessment score (CAUS) including a therapeutic challenge and a multidisciplinary decision-tree algorithm to facilitate search for organic condition and treatment decision making. CAUS provides scores defining whether an autoimmune condition is probably or definitively associated with catatonia (Ferrafiat et al., 2016). This practical clinical tool is the result of our expertise in pediatric catatonia, established through the largest cohort of catatonic youths reported so far and gathered over the last 22 years. We previously detailed the phenomenology and outcome (Cohen et al., 2005; Cornic et al., 2009), the physiopathology(Benarous et al., 2016; Cohen, 2006), the etiologies (Consoli et al., 2012; Ferrafiat et al., 2016; Lahutte et al., 2008) and the treatment (Consoli et al., 2010; Marra et al., 2008; Raffin et al., 2015) of pediatric catatonia. Collaborations with internal medicine, neuro-pediatrics and genetics resulted in proposals in diagnosis and treatment (Consoli et al., 2012; Ferrafiat et al., 2016; Lahutte et al., 2008) for organic catatonia and to the development of the CAUS (Consoli et al., 2012; Ferrafiat et al., 2016; Lahutte et al., 2008) Besides, in this study, the collaboration with a neuro-pediatrics unit for encephalitis allowed us to extent our sample by including patients diagnosed with definite or probable autoimmune encephalitis and who presented catatonia.

In this study, we aim to assess retrospectively the CAUS score (Consoli et al., 2012; Ferrafiat et al., 2016) validity and to define the detection threshold for organic condition versus non-organic condition, using receiver operating characteristic (ROC) analysis on a large sample of child and adolescent catatonia that were carefully investigated for possible organic condition. Also, in the subsample including only autoimmune conditions (definite and probable autoimmune conditions), we aim to assess the CAUS score validity regarding detection of both definite and probable autoimmune encephalitis. To do so, our sample pooled a prospective cohort of child and adolescent catatonia recruited in a psychiatric specialized department, and all individuals with catatonia from a prospective cohort of autoimmune encephalitis recruited in a neuro-pediatric specialized clinic.

2. Method

2.1. Catatonia cohort recruitment

For the purpose of this study, we pooled two prospective samples of children and adolescents with catatonia. The first sample was recruited in a French inpatient department of child and adolescent psychiatry specialized for catatonia ($N = 96$). The second was recruited in an Italian inpatient department of Pediatric Neuroscience specialized in acute encephalopathies ($N = 31$). We briefly summarized how recruitment was performed. For the catatonia sample, every child or adolescent inpatient admitted to the Department of Child and Adolescent Psychiatry at University Hospital La Pitié-Salpêtrière, Paris, France between 1993 and 2015 was systematically assessed for catatonic symptoms. During the time period of the study, 6463 patients aged 4–18 years were hospitalized. The screening for catatonic syndrome follows a two-step procedure. First, at entry or during the course of hospitalization, each patient with a catatonic motor sign (Catalepsy, Waxy flexibility, Stupor, Posturing, Mannerisms, Stereotypies, Echopraxia, Excitement, Staring, Rigidity, Automatic compulsive movements) was examined by one of senior psychiatrists in charge of the study. Regarding catatonic motor symptoms, most of the patients were referred because of extrapyramidal symptoms secondary to antipsychotic prescription and were not eligible.

Second, the diagnosis of catatonic syndrome was made using the Pediatric Catatonia Rating Scale (PCRS) (Benarous et al., 2016) in the presence of at least two catatonic motor symptoms, or one catatonic motor symptom combined with a non-motor symptom (Mutism, Negativism, Echolalia, Verbigeration, Withdrawal, Incontinence, Schizophasia, Acrocyanosis, Autonomic abnormality). PCRS catatonic symptoms are described in Table 1. Catatonia in autism spectrum disorders (ASD) should be diagnosed only if a sharp and sustained increase of these symptoms lasting days or weeks is observed or elicited (Dhossche, 2014; Wing and Shah, 2000).

For the autoimmune encephalitis sample, every child or 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 2015 was systematically assessed for possible autoimmune condition. Catatonia was also systematically search using DSM5 criteria. They include the presence of three symptoms from the following list of twelve: stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerisms, stereotypy, agitation, grimacing, echolalia, and echopraxia. The series comprised 31 patients: 16 patients with anti-NMDA Receptor-encephalitis, 1 paraneoplastic autoimmune encephalitis (anti-HU +), 2 Hashimoto encephalopathy, and 12 with "probable" autoimmune encephalitis (no neuronal antibody detected). None of the patients presented extrapyramidal syndromes secondary to antipsychotics as none of the patients received such a treatment. Indeed patients were admitted directly in a specialized department of Pediatric Neuroscience. Among the 31 patients recruited during the study period, 8 had catatonia and were pooled with the first catatonia sample to increase the number of autoimmune conditions of the cohort. Therefore, the pooled sample included 104 patients (see Fig. 1).

Please cite this article as: Ferrafiat, V., et al., A causality algorithm to guide diagnosis and treatment of catatonia due to autoimmune conditions in children and adolescents, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.06.036

Table 1
Definition of catatonic symptoms in the pediatric catatonia rating scale (PBRS).

Motor symptoms		Non motor symptoms	
Catalepsy	Passive induction of a posture held against gravity	Withdrawal	Refusal to make eye contact and not responding to nonverbal communication
Stupor	Extreme hypoactivity, immobile, minimally responsive to stimuli	Mutism	No, or very little, verbal response, not applicable if there is an established aphasia
Posturing	Active and/or spontaneous maintenance of a posture against gravity	Mannerisms	Odd caricature of normal actions
Waxy flexibility	Slight and even resistance to positioning by examiner	Negativism	Opposing or not responding to instructions or external stimuli
Staring	Fixed gaze, little or visual scanning of environment, decreased blinking	Echolalia	Mimicking another's speech
Echopraxia	Mimicking another's movements	Incontinence	Nocturnal enuresis, daytime urinary incontinence, or fecal incontinence
Stereotypes	Repetitive, abnormally frequent, non-goal directed movements	Verbigeration	Repetition of phrases or sentences, like a scratched record
Excitement	Extreme hyperactivity, constant motor unrest which is apparently non purposeful. Not to be attributed to akathisia or goal directed agitation	Schizophasia	Scrambled speech, word salad, seemingly random words and phrases linked
Automatic compulsive movement	Involuntary muscle activity exhibited in posture, attitudes, mimic or gesture due to inhibition or forced motor action	Acrocyanosis	Cyanosis of the extremities
Rigidity	Maintenance of a rigid position despite efforts to be moved, exclude if cogwheeling or tremor present	Refusal to eat, drink	Severe decrease of daily food or drink intake

2.2. Medical condition search in the catatonia sample recruited in a psychiatric department

To maximize the accuracy of medical diagnoses in the sample of patients with catatonia recruited in a psychiatric department, an internist and a neurologist performed an additional physical examination on all patients. In previous reports, we proposed guidelines for clinical and paraclinical investigations to help determine the medical conditions associated with catatonia (Cornic et al., 2009; 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 to orient towards a diagnosis. We used a multidisciplinary approach with the same medical staff during follow-up. Neurological and global examinations, standardized cognitive/neuropsychological assessments and psychiatric assessments were performed to identify medical conditions. Even if no clinical symptoms (other than catatonia) were present, paraclinical 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. provides a detailed list of these procedures (Lahutte et al., 2008). When fever or acute symptoms were present, we performed cerebrospinal fluid analysis. Other specific investigations

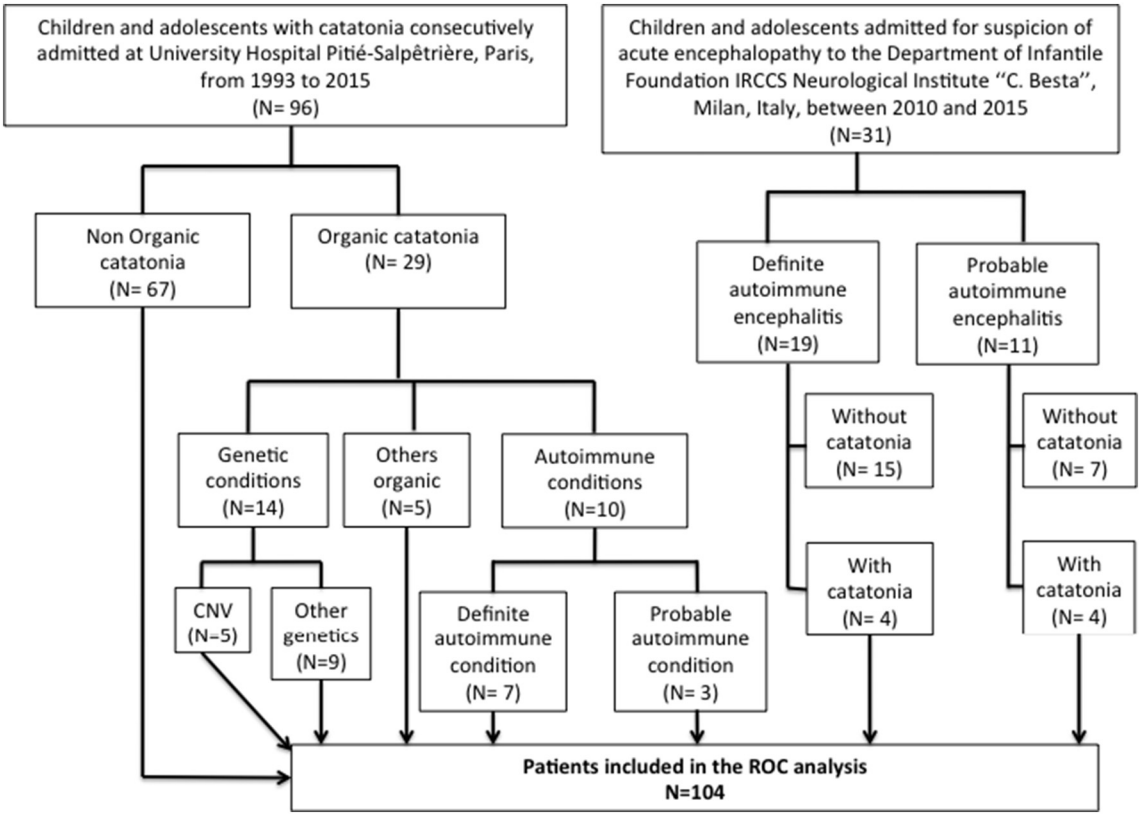

Fig. 1. Flow chart of the study. ROC = receiver operating characteristic; CNV = copy number variation.

Please cite this article as: Ferrafiat, V., et al., A causality algorithm to guide diagnosis and treatment of catatonia due to autoimmune conditions in children and adolescents, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.06.036

were performed under prescription when we found other conditions suggestive of medical or neurological problems.

2.3. Causality assessment method

To assess the causality of the medical risk factors associated with catatonia, we designed a causality assessment score (CAUS) that was detailed in a previous study (Consoli et al., 2012). The score includes 5 items. Each item can be rated from 0 to 2 (0 = absent; 1 = moderate; 2 = high). CAUS scoring was made retrospectively and based on the clinical and paraclinical databases from the two samples. The details of the rating process for a suspected organic condition are detailed in Table 2. To increase detection of autoimmune condition, we include in item 5 a therapeutic challenge. For each patient we systematically searched for and scored retrospectively the following five causality-support criteria on a 3-point scale: (1) the existence of similar cases in the literature since this criteria is important for causality when genetic abnormalities are found; (2) the presence of atypical clinical symptoms (e.g. epilepsy, movement disorder…) or atypical psychiatric symptoms (acute onset psychosis, acute cognitive regression…); (3) the presence of biological symptoms (e.g. antineuronal antibodies, blood or CSF autoimmune markers…); (4) the presence of other paraclinical symptoms (e.g. existence of abnormalities on EEG, PET scan, MRI…); and (5) and response to a specific treatment related to the suspected medical condition (e.g., improvement of catatonia after immunomodulatory treatment). With this procedure, CAUS maximum score was 10. To better improve the CAUS score to detect autoimmune condition, we propose to use a therapeutic challenge with high dosage corticoids test, a common practice in internal medicine when an autoimmune condition is suspected. In case of partial (score = 1) or total (score = 2) improvement, it may confirm the existence of an underlying autoimmune condition and legitimate the use of aggressive immunosuppressive treatments (plasma exchange and second line treatments), even presumptively in young patients with probable autoimmune catatonia. This method appeared promising to catch patients with both probable and definite autoimmune condition in a small series (Ferrafiat et al., 2016). Two raters independently scored the patients' CAUS. The inter-rater reliability was excellent (2 raters, 13 cases; intraclass correlation coefficient = 0.91, [95% confidence interval = 0.86–0.99]).

2.4. 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. Given the binary classification needs, we used receiver operating characteristic (ROC) analysis to assess CAUS validity. We also analyzed confusion matrices. Two different analyses were performed. First, we classified all patients ($N = 104$) according to organic condition or not. We aimed to better define the CAUS threshold for best classification. Our previous study estimated it near a score of 6 (Consoli et al., 2012). Secondly, we classified patients with non-organic condition versus patients with probable and definite autoimmune conditions. We aimed to ensure that narrowing our organic cases to those with autoimmune condition did not dramatically change the classification performance. This second analysis was performed on a subsample including 85 patients.

3. Results

The cohort included 67 cases of non-organic catatonia and 37 cases of organic catatonia (18 autoimmune conditions and 19 other organic conditions). Participants' characteristics are given in Table 3. Autoimmune conditions included Lupus erythematosus ($N = 5$), anti-NMDA Receptor encephalitis ($N = 5$), Hashimoto encephalitis ($N = 1$), and probable autoimmune conditions ($N = 7$). The last were conditions in which clinical and paraclinical criteria (abnormalities of EEG, CSF, immunological investigations…) point to an immunomediated process, but no neuronal antibody was detected. However, to belong to this group, therapeutic challenge with immunosuppressive/modulatory treatment had to be positive. Regarding immunosuppressive treatment, all patients with definite and probable autoimmune condition received a therapeutic challenge with high dosage corticoids pulses. Catatonic features were drastically improved after the challenge, except for one patient who presented a mild response. Catatonia's improvement after corticoids was enhanced by adjunctive plasma exchanges for 6 (75%) patients from the French cohort and Intravenous Immunoglobulin for 6 (75%) patients from the Italian sample. Second line treatments (cyclophosphamide, mycophenolate mofetil, aziathropine) were indicated for 8 patients (100%) from the French cohort, in order to maintained catatonia's improvement after a good response to high dosage corticoids and/or plasma exchanges.

Receiver operating characteristic (ROC) analysis showed that the CAUS performance in discriminating individuals with organic catatonia vs. those without organic catatonia was excellent (Area Under the Curve = 0.99). For a threshold ≥ 5, accuracy was equal to 0.96 (Fig. 2a). Confusion matrices found 100 patients correctly classified, 1 false negative and 3 false positives. Similarly, the CAUS performance in discriminating individuals with probable or definite autoimmune catatonia vs. those without organic catatonia was excellent (AUC = 0.99). For the same

Table 2
Causality Assessment Score (CAUS) rating.

Item 1	The existence of similar cases in the literature	Have other similar cases been reported in the medical literature or in genetic databases?	0 = none 1 = 1 to 4 2 ≥ 5
Item 2	The presence of atypical clinical symptoms or atypical psychiatric signs	Does the patient present any specific non-psychiatric symptoms such as: neurologic (epilepsy, movement disorder), cutaneous (skin rash, alopecia…), ophthalmologic (cataract, uveitis…)? Does the patient present any psychiatric atypical signs such as: acute onset psychosis, resistance to usual treatments, acute cognitive regression	0 = none 1 = few 2 = many
Item 3	The presence of biological symptoms	Does the patient present any biological abnormalities (e.g. antineuronal antibodies, autoimmune blood or CSF markers, lymphocytic pleocytosis, high IgG index, oligoclonal bands)?	0 = none 1 = few 2 = many
Item 4	The presence of other para-clinical symptoms	Existence of (specific or unspecific) abnormalities on any other non-clinical and non-biological test such as EEG signs of encephalitis, PET scan signs of vascularitis, MRI signs of inflammation?	0 = none 1 = few 2 = many
Item 5	Response to a specific therapeutic challenge related to the suspected medical condition	Does the patient improve clinically after receiving a treatment targeting an organic condition? In the case of probable autoimmune condition, does high dosage corticoids improved patient's condition?	0 = no improvement 1 = mild improvement 2 = major improvement
Total	Addition of items 1 to 5 scores		0–10

Please cite this article as: Ferrafiat, V., et al., A causality algorithm to guide diagnosis and treatment of catatonia due to autoimmune conditions in children and adolescents, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.06.036

Table 3
Characteristics of the participants.

	N	Age Mean (SD)	% male	Diagnosis[a]	CAUS score Mean (SD) [range]
Non–organic catatonia	67	14.9 (3.2)	65.6	Schizophrenia: N = 23 Major depression: N = 10 Bipolar disorder: N = 8 Neurodevelopmental disorder[b] : N = 26	} 0.24 (0.88) [0–5] 0.96 (1.56) [0–5]
Organic catatonia	37	14.76 (3.86)	43.3	Total with organic condition: N = 37 Other organic condition: N = 5 Significant CNV: N = 5 Other genetics: N = 9 Autoimmune condition: N = 11 Probable autoimmune condition: N = 7	6.81 (1.65) [4–10] 6.80 (1.64) [5–8] 5.4 (0.55) [5–6] 6.78 (1.86) [4–9] 8.18 (1.33) [5–10] 5.86 (0.9) [5–7]

SD = standard deviation; CNV = common number variation; CAUS = causality score.
[a]Multiple diagnoses are possible due to comorbidity.
[b]Autism spectrum disorder and/or intellectual disability.

threshold, accuracy is equal to 0.96 (fig. 2b). Confusion matrices found 82 patients correctly classified, no false negative and 3 false positives.

4. Discussion

4.1. Detecting autoimmune condition in youths with catatonia

From our previous study (Consoli et al., 2012), we confirm the CAUS performance in discriminating children and adolescents with organic catatonia vs. those without organic catatonia in a larger cohort enriched with cases of catatonia due to autoimmune conditions. The autoimmune conditions such as systemic erythematous lupus, Hashimoto encephalopathy or autoimmune encephalitis are likely to trigger catatonia (Armangue et al., 2012; Ferrafiat et al., 2016; Florance et al., 2009; Honnorat et al., 2013; Lahutte et al., 2008; Lanham et al., 1985; Luca et al., 2011). Therefore, clinicians need to be aware of a possible underlying autoimmune condition when young patients present catatonic features. As we discussed in a previous small series (Ferrafiat et al., 2016), the lack of autoimmune evidence can really be challenging in terms of diagnosis and treatment decision in some young patients with catatonia. Experts now emphasize the encephalitis's diagnostic issues and the idea that the lack of autoimmune markers does not exclude the possibility of an autoimmune disorder (Graus et al., 2016). In order to validate this idea, they proposed three categories of encephalitis to be differentiated: possible autoimmune encephalitis, probable autoimmune encephalitis and definite autoimmune encephalitis. By definite encephalitis, they mean that the evidence of specific and well-characterized antibodies is found. For the probable autoimmune encephalitis, the major point is that the autoantibody status is not found for diagnosis but the neuropsychiatric presentation and paraclinical criteria of specific encephalitis (autoantibodies anti-NMDA receptor encephalitis, acute disseminated encephalomyelitis, limbic encephalitis…) are evident. Also, other defined syndromes with no antibodies can be regarded as autoantibody-negative probable autoimmune encephalitis. This new concept of probable encephalitis represents an interesting classification for patients who present catatonia and acute psychiatric symptoms associated with neurologic symptoms and cognitive impairment and for whom no clear autoimmune evidence is found. Finally, once you have a hypothesis of autoimmune encephalitis but without criteria for either probable or definite autoimmune encephalitis, you have a possible autoimmune encephalitis (Graus et al., 2016). In our cohort, which was started before the Graus et al. report, we had

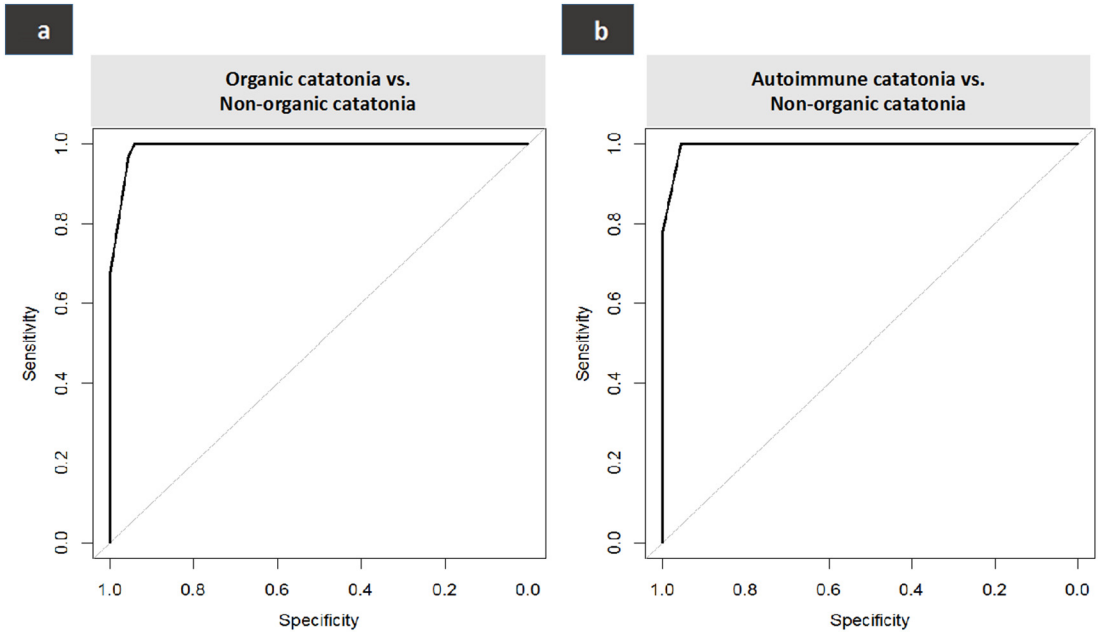

Fig. 2. Receiver operating characteristic (ROC) curve showing the CAUS performance in discriminating individuals with organic catatonia vs. those without organic catatonia (2a) and individuals with autoimmune catatonia vs. those without organic catatonia (2b).

Please cite this article as: Ferrafiat, V., et al., A causality algorithm to guide diagnosis and treatment of catatonia due to autoimmune conditions in children and adolescents, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.06.036

a very similar proposal and used the same concept of "probable" autoimmune encephalitis ($N = 7$). None of these patients have any characterized autoantibodies found in the CSF. However, they all presented an acute onset, neurologic symptoms such as seizures, memory loss, and cognitive regression. Most of them also presented unspecific paraclinical abnormalities (CSF, EEG, MRI, PET-Scan).

As the CAUS implies a large biological and paraclinical screening in its rating process, we reviewed the literature and aim to provide a multidisciplinary explorations panel based on the recent literature and our clinical experience in catatonic patients. When clinicians are dealing with catatonic patients, the main point is to exclude all possible organic conditions including autoimmune ones (Consoli et al., 2012; Lahutte et al., 2008). In a matter of being practical, we decided to only discuss autoimmune explorations, but metabolic and genetic explorations must proceed as a non-negligible number of our catatonic patients ($N = 14$) presented genetic disorders (Consoli et al., 2012). Plasma and CSF are to be explored (Afshari et al., 2012; Dalmau et al., 2011; Dalmau et al., 2008; Dalmau et al., 2007; Honnorat et al., 2013; Levy and Kamphuis, 2012; Nandi-Munshi and Taplin, 2015). The immune explorations are a key point of our algorithm and represent one of the items of the CAUS (Ferrafiat et al., 2016). The distinction between systemic autoimmune disorder and autoimmune encephalitis is important. Indeed, in the first situation, plasma antibodies such as anti-DNA, anti-Sm, anti-TPO, anti-TG are likely to be found positive (Chong et al., 2003; Kamphuis and Silverman, 2010; Levy and Kamphuis, 2012; Montagna et al., 2016). On the other hand, encephalitis suggests abnormalities in the CSF which can be: i) inflammatory and/or autoimmune CSF markers (e.g. presence of high IgG index or oligoclonal bands); ii) well-characterized antibodies found in the CSF (e.g. anti-NMDA, anti-GABA a/c, anti-Hu, anti-Yo) (Florance et al., 2009; Hacohen et al., 2013; Luca et al., 2011; Titulaer et al., 2013). EEG is also interesting for the presence of "delta brushes" activity or focal/diffuse slow activity (Britton et al., 2015; Schmitt et al., 2012; Sejvar et al., 2007; Venkatesan et al., 2013). Brain imaging as head-CT and MRI are also useful in order to exclude vascular, infectious, and neurodegenerative disorders. A PET-scan may show hypometabolism compatible with encephalitis and vascularitis. The entire panel is summed up in Fig. 3.

Regarding autoimmune encephalitis treatment options, the literature gathers numerous data, and all studies conclude to the same need to introduce immunosuppressive treatment as early as possible in order to limit neurocognitive sequels (Armangue et al., 2012; Byrne et al., 2015; Chapman and Vause, 2011; Florance et al., 2009; Luca et al., 2011; Nosadini et al., 2015; Titulaer et al., 2012). Indeed, the delay of introducing the specific treatment may lead to chronic catatonia and significant cognitive impairment. When it comes to treatment options, we have to consider two types of line: 1) the first line includes corticoids, plasma exchange (PE) and intravenous immunoglobulins; and 2) the second line are immunosuppressive medications such as rituximab, cyclophosphamide and mycophenolate mofetil. Even if there are no international guidelines for children and adolescents in the choice of medication, many studies suggest the use of high dosage corticoids via pulses at first (Armangue et al., 2012; Brunner et al., 2008; Levy and Kamphuis, 2012; Luca et al., 2011), as most of the youth present good response rates. In lupus and anti-NMDA receptor encephalitis, PE and their peripheral action represent an interesting option (Boers and Colebatch, 2001; DeSena et al., 2015; Hussain et al., 2005; Prytuła et al., 2015; Suppiej et al., 2016) and provide an efficient treatment for catatonia (Elia et al., 2005; Ferrafiat et al., 2016; Marra et al., 2008). When it

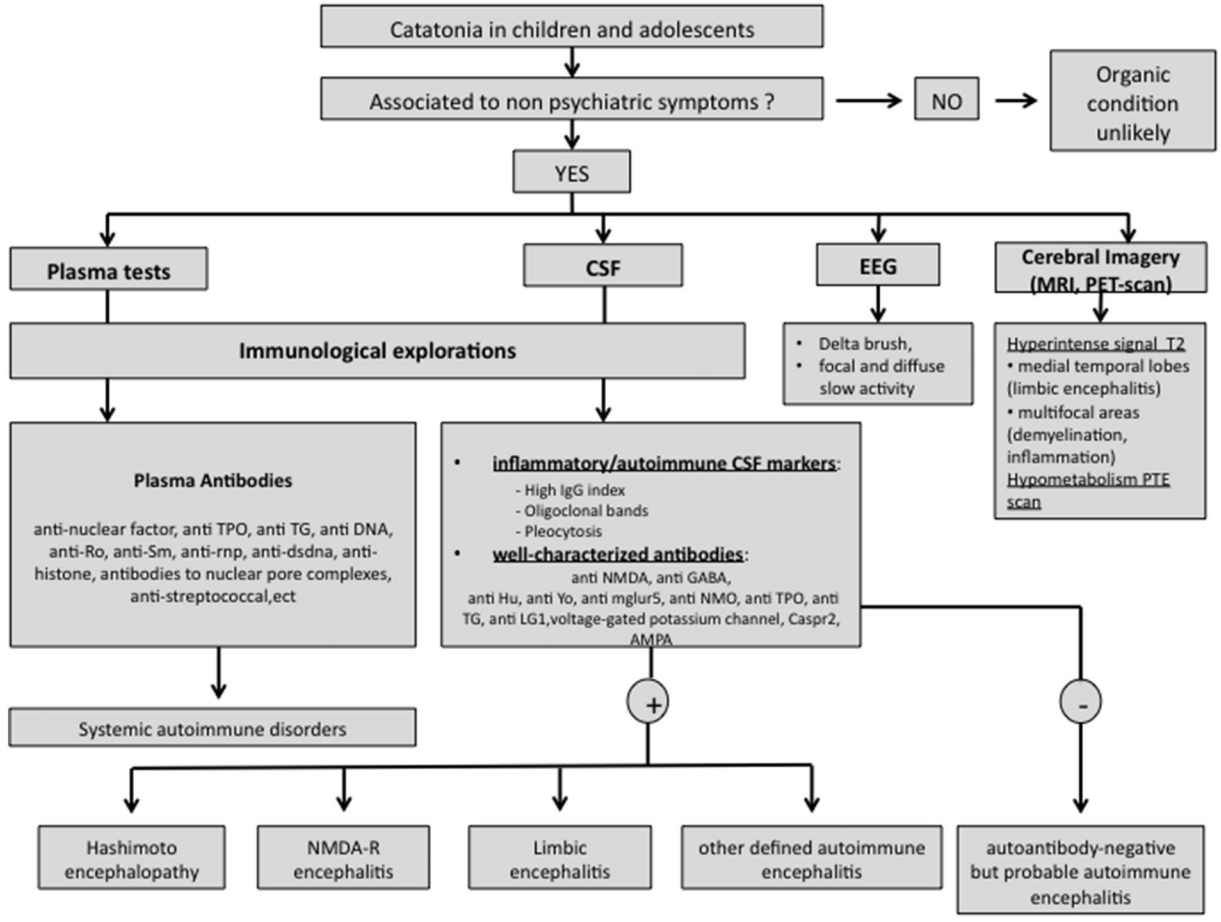

Fig. 3. Biological and paraclinical explorations proposed for autoimmune catatonic patients. CSF = cerebral spinal fluid; EEG = electroencephalogram; TPO = thyroperoxydase; TG = thyroglobulin; IgG = immunoglobulin G; MRI = Magnetic Resonance Imaging.

Please cite this article as: Ferrafiat, V., et al., A causality algorithm to guide diagnosis and treatment of catatonia due to autoimmune conditions in children and adolescents, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.06.036

is an adjunct to corticoids, PE may enhance corticoids efficacy (DeSena et al., 2015; Suppiej et al., 2016). In case of resistance to the first lines (30% to 40% of patients) (Armangue et al., 2012) or relapses, second lines are to be considered (Byrne et al., 2015; Florance et al., 2009; Titulaer et al., 2012; Zekeridou et al., 2015). It appears to be beneficial to precociously prescribe second lines in children and adolescents in order to be efficient as soon as possible and hence to ensure better outcomes (Frankovich et al., 2015; Ishiura et al., 2008; Luca et al., 2011). In their study, Zekeridou et al. used second-line immunotherapy, especially Rituximab, more frequently than other previous studies (83 vs 14–35%) for anti-NMDA encephalitis (Zekeridou et al., 2015), skipping rapidly the first lines and following recommendation of the French Paraneoplastic Neurologic Syndromes (PNS) Reference Center. Rituximab is increasingly being considered as a first-line therapy (Dale et al., 2012). 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). Regardless of the treatment decision habits and the lack of treatment guidelines, aggressive immunosuppressive treatment is to be considered when facing definite autoimmune catatonia, even presumptively in case of a probable autoimmune catatonia resistant to standard symptomatic treatments.

Regarding catatonia symptomatic treatment, we previously reported how patients responded to treatment in a subsample of 66 French youths. In total 51 (77%) patients underwent a benzodiazepine (BZD) trial that was effective in 33 (65%) patients. Other treatments included ECT ($N = 12$, 18%); antipsychotic medications, mostly in combination; and treatment of an underlying medical condition, when possible. The treatment response was independent of the underlying psychiatric or systemic medical condition (Raffin et al., 2015). Regarding those with autoimmune conditions reported here, all received as first line treatment high dosage of BZD until immunosuppressive treatments were initiated. None of them required ECT. To our opinion benzodiazepines must be introduced as soon as the diagnosis of catatonia is validated, and maintained until etiological treatment (immunosuppressive treatment) is started and shows its efficacy (Fig. 4). In some cases with lupus or anti-NMDA encephalitis described in the literature (Bica et al., 2015; Coffey and Cooper, 2016), catatonic features might poorly respond to immunosuppressive treatment and may remain present despite the proper etiological treatment. These complex situations could be explained by: i) a chronic and/or resistant aspect of catatonia which requires the use of ECT (Consoli et al., 2010; Dhossche, 2014; Raffin et al., 2015); ii) a resistance to first line treatment (corticoids or immunoglobulin) which often occurs in youth (Florance et al., 2009; Kamphuis and Silverman, 2010; Titulaer et al., 2013); iii) the lack of access to plasma exchanges which can drastically improve autoimmune catatonia (Ferrafiat et al., 2016; Marra et al., 2008; Suppiej et al., 2016); and iv) an unknown or underestimated underlying condition which also triggers catatonia despite patient's autoimmune backgrounds.

Because of the biological and paraclinical difficulties to make the proper diagnosis, we developed the CAUS (Consoli et al., 2012; Ferrafiat et al., 2016) so clinicians could benefit from it as a practical clinical diagnosis tool. In our previous study, we estimated the threshold around 6 but it was from a clinical point of view (Ferrafiat et al., 2016). By using a classification approach on a large sample including 18 cases

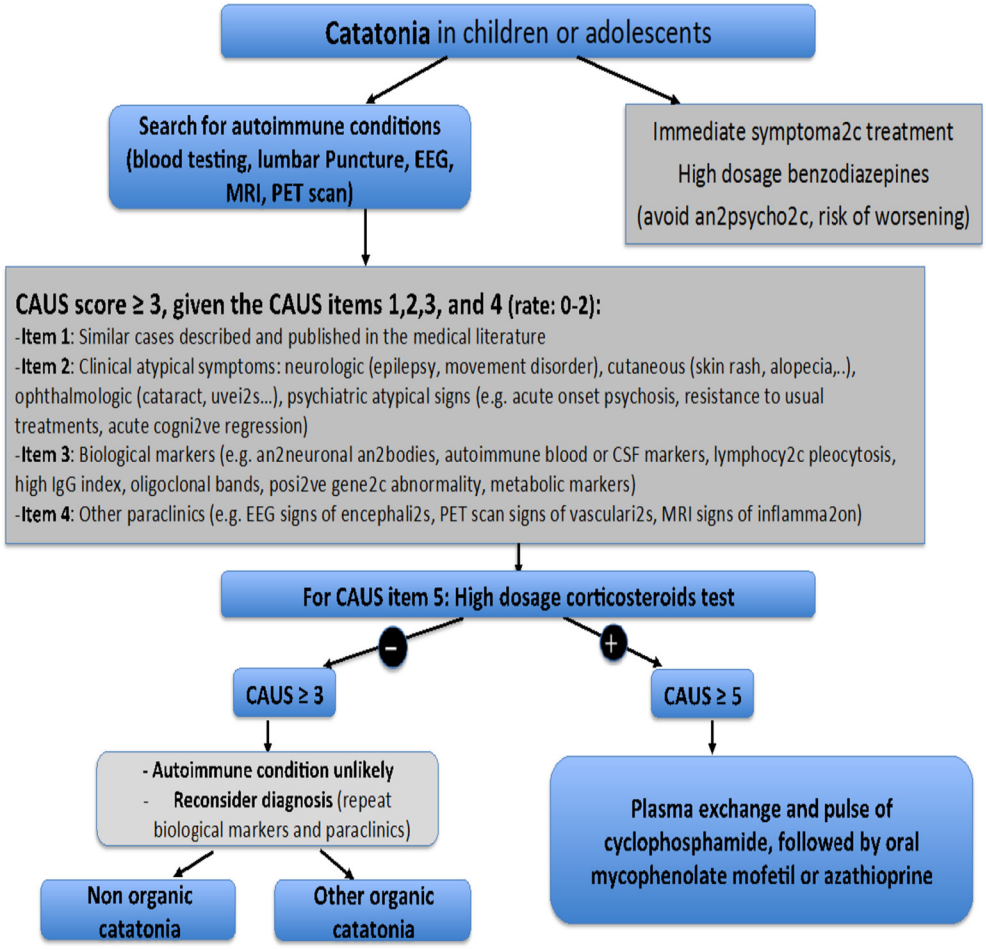

Fig. 4. Step by step causality score including immunosuppressive challenge for young patients with catatonia. CSF = cerebral spinal fluid; EEG = electroencephalogram; IgG = immunoglobulin G; MRI = Magnetic Resonance Imaging; CAUS = causality score.

Please cite this article as: Ferrafiat, V., et al., A causality algorithm to guide diagnosis and treatment of catatonia due to autoimmune conditions in children and adolescents, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.06.036

of probable and definite autoimmune condition, we refined the threshold to be equal to 5. This helped modify our diagnostic and treatment algorithm with a step by step approach. After rating the first four items, if this CAUS pre-score is equal or up to 3, it is the equivalent of a possible autoimmune catatonia. Then, the response to high dosage corticoids, as a therapeutic challenge, leads to a final score of 5 or up and legitimate the use of immunosuppressive treatment (PE and/or second lines) for probable encephalitis. Taking this proposal into account, our previous diagnostic and treatment algorithm (Ferrafiat et al., 2016) has been modified and is shown in Fig. 4.

4.2. Limitations and strengths

The results of this study should be interpreted in the context of its limitations. First, the number of subjects recruited was low, despite the 23-year recruitment period. This could be explained by the very low prevalence of catatonia in youths compared to other psychiatric disorders (Cohen et al., 2005). Second, to increase the number of patients with probable and/or definite autoimmune encephalitis we grouped two different samples that have specific recruitment bias. Third, our study presents sources of heterogeneity that may not be generalizable. In this study, we used two clinical samples of acutely ill patients recruited in two university teaching hospitals that may be particularly enriched in subjects with a more severe form of catatonia and including both organic and psychiatric catatonia. Fourth, ROC analysis was performed to better define the CAUS threshold and to adequately differentiate youths with organic or autoimmune catatonia from youths with non-organic catatonia. However, the validity of the CAUS in screening organic catatonia among inpatient youths with catatonia would require that all subjects were selected in a similar process (Peacock and Peacock, 2010). Also, even if the two pooled samples were recruited prospectively, CAUS score was rated retrospectively based on data base information. Although inter-rater reliability was excellent, CAUS application in absence of blind conditions regarding the final diagnosis represents a potential bias that likely inflates its discriminative power. Besides, prospective use of CAUS rating would have been better. Finally, we cannot exclude the possibility that some patients with positive autoimmune markers are present among our non-organic catatonic French cohort, as the recruitment started before the development of neuro-immune exploration assays. The strengths of this study include (i) the large amount of data and the prospective design, (ii) the recruitment of participants over a 23-year period, (iii) the length of hospitalization during which patients were assessed and treated, (iv) the fact that this sample is the largest in the literature, (v) the comparison of patients with organic catatonia to patients with non-organic catatonia, and (vi) the potential impact of the CAUS in terms of therapeutic decision making.

5. Conclusion

To conclude, our study findings have several clinical implications for catatonic youth. Catatonia in children and adolescents is characterized by a high frequency of organic conditions (Consoli et al., 2012; Lahutte et al., 2008). Autoimmune conditions represent a diagnostic and therapeutic challenge because specific treatments can be drastically efficient on catatonia (Ferrafiat et al., 2016; Marra et al., 2008) and the timing of treatment initiation can limit neurological and cognitive sequels (Armangue et al., 2012; Byrne et al., 2015; Finke et al., 2012; Titulaer et al., 2013). We emphasize the importance and need to ensure an early diagnosis of the underlying autoimmune condition via the identification of antibodies in CSF. When no biological evidence of an autoimmune disorder is identified, the use of the CAUS score algorithm derived from a multidisciplinary assessment, a high dosage corticoids therapeutic challenge and a threshold ≥ 5 may help in diagnosing and treating autoimmune related conditions even in the absence of formal identification of autoantibodies, and in deciding early and aggressive use of immunosuppressive or immune-modulatory treatment, including plasma exchange, in the context of juvenile catatonia.

Funding source

This study was done with no specific support. The authors have no financial relationships relevant to this article to disclose.

Contributors

Study concept and design: Ferrafiat, Cohen, Consoli, Amoura, Haroche, and Gerardin.
Acquisition and collecting data: Ferrafiat, Freri, Raffin, Cohen, Granata, Nardocci, Consoli, Zibordi, Viaux, Benarous, Riquin, Olliac, and Xavier.
Statistical analysis: Bodeau and Cohen.
Interpretation of data: All authors.
Drafting the manuscript: Ferrafiat, Freri, Raffin, Amoura, Cohen, and Consoli.
Critical revision of the manuscript for important intellectual content: Amoura, Cohen, and Consoli.
Final draft: All authors.

Conflicts of interest

The authors have no conflicts of interest relevant to this article to disclose.

Acknowledgement

Authors thank Dr. Angela Vincent, Dr. Tom Pollak and Dr. Monique Ernst for in depth comments on an earlier version of this manuscript.

References

Afshari, M., Afshari, Z.S., Schuele, S.U., 2012. Pearls & oysters: Hashimoto encephalopathy. Neurology 78:e134–e137. http://dx.doi.org/10.1212/WNL.0b013e3182582fd4.
Armangue, T., Petit-Pedrol, M., Dalmau, J., 2012. Autoimmune encephalitis in children. J. Child Neurol. 27:1460–1469. http://dx.doi.org/10.1177/0883073812448838.
Benarous, X., Consoli, A., Raffin, M., Bodeau, N., Giannitelli, M., Cohen, D., Olliac, B., 2016. Validation of the Pediatric Catatonia Rating Scale (PCRS). Schizophr. Res. http://dx.doi.org/10.1016/j.schres.2016.06.020.
Bica, B.E.R.G., Moro, A.L.D., Hax, V., Nicol, N.A., Campos, G.S., Rivera, L.M.S., da Costa, A.F.C., Xavier, R.M., Monticielo, O.A., 2015. Electroconvulsive therapy as a treatment for refractory neuropsychiatric lupus with catatonia: three case studies and literature review. Lupus 24:1327–1331. http://dx.doi.org/10.1177/0961203315585816.
Boers, P.M., Colebatch, J.G., 2001. Hashimoto's encephalopathy responding to plasmapheresis. J. Neurol. Neurosurg. Psychiatry 70, 132.
Britton, P.N., Eastwood, K., Paterson, B., Durrheim, D.N., Dale, R.C., Cheng, A.C., Kenedi, C., Brew, B.J., Burrow, J., Nagree, Y., Leman, P., Smith, D.W., Read, K., Booy, R., Jones, C.A., Australasian Society of Infectious Diseases (ASID), Australasian College of Emergency Medicine (ACEM), Australian and New Zealand Association of Neurologists (ANZAN), Public Health Association of Australia (PHAA), 2015. Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. Intern. Med. J. 45:563–576. http://dx.doi.org/10.1111/imj.12749.
Brunner, H.I., Gladman, D.D., Ibañez, D., Urowitz, M.D., Silverman, E.D., 2008. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. Arthritis Rheum. 58:556–562. http://dx.doi.org/10.1002/art.23204.
Byrne, S., Walsh, C., Hacohen, Y., Muscal, E., Jankovic, J., Stocco, A., Dale, R.C., Vincent, A., Lim, M., King, M., 2015. Earlier treatment of NMDAR antibody encephalitis in children results in a better outcome. Neurol. Neuroimmunol. Neuroinflamm. 2, e130. http://dx.doi.org/10.1212/NXI.0000000000000130.
Chapman, M.R., Vause, H.E., 2011. Anti-NMDA receptor encephalitis: diagnosis, psychiatric presentation, and treatment. Am. J. Psychiatry 168:245–251. http://dx.doi.org/10.1176/appi.ajp.2010.10020181.
Chong, J.Y., Rowland, L.P., Utiger, R.D., 2003. Hashimoto encephalopathy: syndrome or myth? Arch. Neurol. 60, 164–171.
Coffey, M.J., Cooper, J.J., 2016. Electroconvulsive therapy in anti-N-methyl-D-aspartate receptor encephalitis: a case report and review of the literature. J. ECT 32:225–229. http://dx.doi.org/10.1097/YCT.0000000000000334.
Cohen, D., 2006. Towards a valid nosography and psychopathology of catatonia in children and adolescents. Int. Rev. Neurobiol. 72:131–147. http://dx.doi.org/10.1016/S0074-7742(05)72008-0.
Cohen, D., Nicolas, J.-D., Flament, M.F., Périsse, 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. 76:301–308. http://dx.doi.org/10.1016/j.schres.2005.01.014.
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 26:259–265. http://dx.doi.org/10.1097/YCT.0b013e3181fb3924.
Consoli, A., Raffin, M., Laurent, C., Bodeau, N., Campion, D., Amoura, Z., Sedel, F., An-Gourfinkel, I., Bonnot, O., Cohen, D., 2012. Medical and developmental risk factors of catatonia in children and adolescents: a prospective case-control study. Schizophr. Res. 137:151–158. http://dx.doi.org/10.1016/j.schres.2012.02.012.

Cornic, F., Consoli, A., Tanguy, M.-L., Bonnot, O., Périsse, 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: 233–240. http://dx.doi.org/10.1016/j.schres.2009.04.021.

Dale, R.C., Merheb, V., Pillai, S., Wang, D., Cantrill, L., Murphy, T.K., Ben-Pazi, H., Varadkar, S., Aumann, T.D., Horne, M.K., Church, A.J., Fath, T., Brilot, F., 2012. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. Brain J. Neurol. 135:3453–3468. http://dx.doi.org/10.1093/brain/aws256.

Dale, R.C., Brilot, F., Duffy, L.V., Twilt, M., Waldman, A.T., Narula, S., Muscal, E., Deiva, K., Andersen, E., Eyre, M.R., Eleftheriou, D., Brogan, P.A., Kneen, R., Alper, G., Anlar, B., Wassmer, E., Heineman, K., Hemingway, C., Riney, C.J., Kornberg, A., Tardieu, M., Stocco, A., Banwell, B., Gorman, M.P., Benseler, S.M., Lim, M., 2014. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology 83:142–150. http://dx.doi.org/10.1212/WNL.0000000000000570.

Dalmau, J., Tüzün, E., Wu, H., Masjuan, J., Rossi, J.E., Voloschin, A., Baehring, J.M., Shimazaki, H., Koide, R., King, D., Mason, W., Sansing, L.H., Dichter, M.A., Rosenfeld, M.R., Lynch, D.R., 2007. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann. Neurol. 61:25–36. http://dx.doi.org/10.1002/ana.21050.

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. 7:1091–1098. http://dx.doi.org/10.1016/S1474-4422(08)70224-2.

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. 10:63–74. http://dx.doi.org/10.1016/S1474-4422(10)70253-2.

DeSena, A.D., Noland, D.K., Matevosyan, K., King, K., Phillips, L., Qureshi, S.S., Greenberg, B.M., Graves, D., 2015. Intravenous methylprednisolone versus therapeutic plasma exchange for treatment of anti-N-methyl-D-aspartate receptor antibody encephalitis: a retrospective review. J. Clin. Apher. 30:212–216. http://dx.doi.org/10.1002/jca.21363.

Dhossche, D.M., 2014. Decalogue of catatonia in autism spectrum disorders. Front. Psych. 5:157. http://dx.doi.org/10.3389/fpsyt.2014.00157.

Dimitri, D., Jehel, L., Dürr, A., Lévy-Soussan, M., Andreux, V., Laplanche, J.-L., Fossati, P., Cohen, D., 2006. Fatal familial insomnia presenting as psychosis in an 18-year-old man. Neurology 67:363–364. http://dx.doi.org/10.1212/01.wnl.0000225181.98341.74.

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 44:1145–1150. http://dx.doi.org/10.1097/01.chi.0000179056.54419.5e.

Ferrafiat, V., Raffin, M., Deiva, K., Salle-Collemiche, X., Lepine, A., Spodenkiewicz, M., Michelet, I., Haroche, J., Amoura, Z., Gerardin, P., Cohen, D., Consoli, A., 2016. Catatonia and autoimmune conditions in children and adolescents: should we consider a therapeutic challenge? J. Child Adolesc. Psychopharmacol. http://dx.doi.org/10.1089/cap.2015.0086.

Finke, C., Kopp, U.A., Prüss, H., Dalmau, J., Wandinger, K.-P., Ploner, C.J., 2012. Cognitive deficits following anti-NMDA receptor encephalitis. J. Neurol. Neurosurg. Psychiatry 83:195–198. http://dx.doi.org/10.1136/jnnp-2011-300411.

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. 66:11–18. http://dx.doi.org/10.1002/ana.21756.

Frankovich, J., Thienemann, M., Rana, S., Chang, K., 2015. Five youth with pediatric acute-onset neuropsychiatric syndrome of differing etiologies. J. Child Adolesc. Psychopharmacol. 25:31–37. http://dx.doi.org/10.1089/cap.2014.0056.

Graus, F., Titulaer, M.J., Balu, R., Benseler, S., Bien, C.G., Cellucci, T., Cortese, I., Dale, R.C., Gelfand, J.M., Geschwind, M., Glaser, C.A., Honnorat, J., Höftberger, R., Iizuka, T., Irani, S.R., Lancaster, E., Leypoldt, F., Prüss, H., Rae-Grant, A., Reindl, M., Rosenfeld, M.R., Rostásy, K., Saiz, A., Venkatesan, A., Vincent, A., Wandinger, K.-P., Waters, P., Dalmau, J., 2016. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 15:391–404. http://dx.doi.org/10.1016/S1474-4422(15)00401-9.

Hacohen, Y., Wright, S., Waters, P., Agrawal, S., Carr, L., Cross, H., De Sousa, C., Devile, C., Fallon, P., Gupta, R., Hedderly, T., Hughes, E., Kerr, T., Lascelles, K., Lin, J.-P., Philip, S., Pohl, K., Prabahkar, P., Smith, M., Williams, R., Clarke, A., Hemingway, C., Wassmer, E., Vincent, A., Lim, M.J., 2013. Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. J. Neurol. Neurosurg. Psychiatry 84: 748–755. http://dx.doi.org/10.1136/jnnp-2012-303807.

Honnorat, J., Didelot, A., Karantoni, E., Ville, D., Ducray, F., Lambert, L., Deiva, K., Garcia, M., Pichit, P., Cavillon, G., Rogemond, V., DeLattre, J.-Y., Tardieu, M., 2013. Autoimmune limbic encephalopathy and anti-Hu antibodies in children without cancer. Neurology 80:2226–2232. http://dx.doi.org/10.1212/WNL.0b013e318296e9c3.

Hussain, N.S., Rumbaugh, J., Kerr, D., Nath, A., Hillis, A.E., 2005. Effects of prednisone and plasma exchange on cognitive impairment in Hashimoto encephalopathy. Neurology 64:165–166. http://dx.doi.org/10.1212/01.WNL.0000148580.98997.C5.

Ishiura, H., Matsuda, S., Higashihara, M., Hasegawa, M., Hida, A., Hanajima, R., Yamamoto, T., Shimizu, J., Dalmau, J., Tsuji, S., 2008. Response of anti-NMDA receptor encephalitis without tumor to immunotherapy including rituximab. Neurology 71:1921–1923. http://dx.doi.org/10.1212/01.wnl.0000336648.43562.59.

Kamphuis, S., Silverman, E.D., 2010. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat. Rev. Rheumatol. 6:538–546. http://dx.doi.org/10.1038/nrrheum.2010.121.

Kashyape, P., Taylor, E., Ng, J., Krishnakumar, D., Kirkham, F., Whitney, A., 2012. Successful treatment of two paediatric cases of anti-NMDA receptor encephalitis with cyclophosphamide: the need for early aggressive immunotherapy in tumour negative paediatric patients. Eur. J. Paediatr. Neurol. EJPN Off. J. Eur. Paediatr. Neurol. Soc. 16:74–78. http://dx.doi.org/10.1016/j.ejpn.2011.07.005.

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. Neuro-Psychopharmacol. Biol. Psychiatry 32:1393–1398. http://dx.doi.org/10.1016/j.pnpbp.2008.02.015.

Lanham, J.G., Brown, M.M., Hughes, G.R., 1985. Cerebral systemic lupus erythematosus presenting with catatonia. Postgrad. Med. J. 61, 329–330.

Levy, D.M., Kamphuis, S., 2012. Systemic lupus erythematosus in children and adolescents. Pediatr. Clin. N. Am. 59:345–364. http://dx.doi.org/10.1016/j.pcl.2012.03.007.

Luca, N., Daengsuwan, T., Dalmau, J., Jones, K., deVeber, G., Kobayashi, J., Laxer, R.M., Benseler, S.M., 2011. Anti-N-methyl-D-aspartate receptor encephalitis: a newly recognized inflammatory brain disease in children. Arthritis Rheum. 63:2516–2522. http://dx.doi.org/10.1002/art.30437.

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: 195–196. http://dx.doi.org/10.1159/000120280.

Montagna, G., Imperiali, M., Agazzi, P., D'Aurizio, F., Tozzoli, R., Feldt-Rasmussen, U., Giovanella, L., 2016. Hashimoto's encephalopathy: a rare proteiform disorder. Autoimmun. Rev. http://dx.doi.org/10.1016/j.autrev.2016.01.014.

Nandi-Munshi, D., Taplin, C.E., 2015. Thyroid-related neurological disorders and complications in children. Pediatr. Neurol. 52:373–382. http://dx.doi.org/10.1016/j.pediatrneurol.2014.12.005.

Nosadini, M., Mohammad, S.S., Ramanathan, S., Brilot, F., Dale, R.C., 2015. Immune therapy in autoimmune encephalitis: a systematic review. Expert. Rev. Neurother. 15: 1391–1419. http://dx.doi.org/10.1586/14737175.2015.1115720.

Peacock, J., Peacock, P., 2010. Oxford Handbook of Medical Statistics. Oxford University Press.

Prytuła, A., Vande Walle, J., Verhelst, H., Eloot, S., Claus, S., De Jaeger, A., Dehoorne, J., Raes, A., 2015. Therapeutic plasma exchange in children with acute autoimmune central nervous system disorders. Int. J. Artif. Organs 38:494–500. http://dx.doi.org/10.5301/ijao.5000435.

Puffer, C.C., Wall, C.A., Huxsahl, J.E., Frye, M.A., 2016. A 20 year practice review of electroconvulsive therapy for adolescents. J. Child Adolesc. Psychopharmacol. 26:632–636. http://dx.doi.org/10.1089/cap.2015.0139.

Raffin, M., Zugaj-Bensaou, L., Bodeau, N., Milhiet, V., Laurent, C., Cohen, D., Consoli, A., 2015. Treatment use in a prospective naturalistic cohort of children and adolescents with catatonia. Eur. Child Adolesc. Psychiatry 24:441–449. http://dx.doi.org/10.1007/s00787-014-0595-y.

Schmitt, S.E., Pargeon, K., Frechette, E.S., Hirsch, L.J., Dalmau, J., Friedman, D., 2012. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 79:1094–1100. http://dx.doi.org/10.1212/WNL.0b013e3182698cd8.

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. 30:631–641. http://dx.doi.org/10.1007/s10545-007-0661-4.

Sejvar, J.J., Kohl, K.S., Bilynsky, R., Blumberg, D., Cvetkovich, T., Galama, J., Gidudu, J., Katikaneni, L., Khuri-Bulos, N., Oleske, J., Tapiainen, T., Wiznitzer, M., Brighton Collaboration Encephalitis Working Group, 2007. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 25: 5771–5792. http://dx.doi.org/10.1016/j.vaccine.2007.04.060.

Suppiej, A., Nosadini, M., Zuliani, L., Pelizza, M.F., Toldo, I., Bertossi, C., Tison, T., Zoccarato, M., Marson, P., Giometto, B., Dale, R.C., Sartori, S., 2016. Plasma exchange in pediatric anti-NMDAR encephalitis: a systematic review. Brain and Development http://dx.doi.org/10.1016/j.braindev.2016.01.009.

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, 200–203.

Titulaer, M.J., McCracken, L., Gabilondo, I., Armangué, T., Glaser, C., Iizuka, T., Honig, L.S., Benseler, S.M., Kawachi, I., Martinez-Hernandez, E., Aguilar, E., Gresa-Arribas, N., Ryan-Florance, N., Torrents, A., Saiz, A., Rosenfeld, M.R., Balice-Gordon, R., Graus, F., Dalmau, J., 2013. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 12:157–165. http://dx.doi.org/10.1016/S1474-4422(12)70310-1.

Titulaer, M.J., McCracken, L., Gabilondo, I., et al., 2012. Clinical features, treatment and outcome of 500 patients with anti-NMDA receptor encephalitis. Neurology.

Venkatesan, A., Tunkel, A.R., Bloch, K.C., Lauring, A.S., Sejvar, J., Bitnun, A., Stahl, J.-P., Mailles, A., Drebot, M., Rupprecht, C.E., Yoder, J., Cope, J.R., Wilson, M.R., Whitley, R.J., Sullivan, J., Granerod, J., Jones, C., Eastwood, K., Ward, K.N., Durrheim, D.N., Solbrig, M.V., Guo-Dong, L., Glaser, C.A., International Encephalitis Consortium, 2013. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 57:1114–1128. http://dx.doi.org/10.1093/cid/cit458.

Wing, L., Shah, A., 2000. Catatonia in autistic spectrum disorders. Br. J. Psychiatry J. Ment. Sci. 176, 357–362.

Zekeridou, A., Karantoni, E., Viaccoz, A., Ducray, F., Gitiaux, C., Villega, F., Deiva, K., Rogemond, V., Mathias, E., Picard, G., Tardieu, M., Antoine, J.-C., Delattre, J.-Y., Honnorat, J., 2015. Treatment and outcome of children and adolescents with N-methyl-D-aspartate receptor encephalitis. J. Neurol. 262:1859–1866. http://dx.doi.org/10.1007/s00415-015-7781-9.

Zuliani, L., Graus, F., Giometto, B., Bien, C., Vincent, A., 2012. Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition. J. Neurol. Neurosurg. Psychiatry 83:638–645. http://dx.doi.org/10.1136/jnnp-2011-301237.

Please cite this article as: Ferrafiat, V., et al., A causality algorithm to guide diagnosis and treatment of catatonia due to autoimmune conditions in children and adolescents, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.06.036