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