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Catatonia Secondary to Anti-N-Methyl-D-Aspartate (NMDA) Receptor Encephalitis

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Orientado por:

João Carlos Pereira Gama Marques

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ABSTRACT

Anti-N-Methyl-D-Aspartate receptor encephalitis (anti-NDMAr encephalitis) is a relatively recent autoimmune entity, as it was first described in 2007. Since then, the exponential publication of clinical cases has led to believe that the disease may not be rare.

Given that it is a condition with neuropsychiatric symptoms, its initial symptom is frequently psychiatric in nature. Hence, psychiatrists are often the first physicians to assess these patients and, as so, must recognized this type of encephalitis as a possible cause for a psychiatric presentation. Catatonia may be inaugural or develop throughout the course of the disease. Management of catatonia secondary to anti-NMDAr encephalitis is based on etiologic treatment of the underlying encephalitis with immunotherapy and removal of the associated tumor, if any.

However, these patients may have variable responses to etiologic treatment, sometimes with catatonic symptoms refractory to both immunotherapy and benzodiazepines, which attests to the necessary urgency to know how to manage these patients. Medical literature regarding the management of psychiatric symptoms due to medical illnesses is scarce. In the clinical setting, physicians appear to be using guidelines originally created to address the management of catatonia due to primary psychiatric conditions.

In this literature review, catatonia was historically contextualized and anti-NMDAr encephalitis overall described. Clinical cases pertaining to the management of catatonia secondary to this type of encephalitis were described and discussed throughout this review and summarized in a table at the end.

This research has highlighted electroconvulsive therapy (ECT) as the most frequently cited option for the management of the patient with catatonia secondary to anti-NMDAr encephalitis refractory to etiologic treatment of the underlying condition and symptomatic treatment with benzodiazepines, with the analyzed cases reporting safe, effective and favorable outcomes for patients. In February 2019, a systematic revision of the use of ECT in these patients corroborated these conclusions.

Keywords: anti-NMDA receptor encephalitis; catatonia; secondary catatonia; electroconvulsive therapy; neuropsychiatry.

The Final Work expresses the author's opinion and not the opinion of Faculdade de Medicina de Lisboa.

RESUMO

A encefalite por anticorpos anti-recetor N-Metil-D-Aspartato (encefalite anti-NMDAr) é uma entidade autoimune relativamente recente, tendo sido descrita pela primeira vez em 2007. Desde então, a exponencial publicação de casos clínicos referentes à mesma leva a crer que a doença não seja rara.

Dado ser uma patologia com sintomatologia neuropsiquiátrica, o sintoma inaugural desta doença é frequentemente psiquiátrico, sendo o psiquiatra o primeiro médico a avaliar estes doentes, pelo que este deve reconhecer este tipo de encefalite como causa possível para uma apresentação psiquiátrica. A catatonia pode ser inaugural ou desenvolver-se durante o curso da doença. A gestão do doente com encefalite anti-NMDAr centra-se no seu tratamento etiológico (imunoterapia) e remoção do eventual tumor associado.

No entanto, a resposta de doentes ao tratamento etiológico é variável, com sintomas catatónicos refratários tanto à imunoterapia como a benzodiazepinas, pelo que a gestão desta se torna imperiosa. A literatura com enfoque na gestão da sintomatologia psiquiátrica em contexto de doença orgânica é, contudo, escassa. Na prática clínica, a gestão da catatonia parece guiar-se por *guidelines* criadas para patologia psiquiátrica primária.

Nesta revisão da literatura, procurou-se contextualizar historicamente a catatonia e fazer uma descrição geral da encefalite em questão, terminando com a informação encontrada acerca da catatonia secundária à mesma.

Na pesquisa realizada, a terapia eletroconvulsiva surgiu como a opção mais frequentemente citada para a gestão do doente com catatonia secundária a encefalite anti-NMDAr refratária ao tratamento etiológico da encefalite subjacente e ao tratamento sintomático com benzodiazepinas, com os casos analisados a reportar resultados seguros, eficazes e favoráveis para os doentes. Em fevereiro de 2019, uma revisão sistemática do uso da terapia eletroconvulsiva nestes doentes veio corroborar estas conclusões.

Palavras-chave: encefalite anti-recetor NMDA; catatonia; catatonia secundária; terapia elotroconvulsiva; neuropsiquiatria.

O Trabalho Final exprime a opinião do autor e não da Faculdade de Medicina de Lisboa.

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INTRODUCTION

Catatonia is a psychiatric symptom frequently involved in organic illnesses and often the reason why psychiatrists are asked to intervene in the management of patients in medical wards.

One of the many organic diseases that is associated with catatonic symptoms is anti-N-Methyl-D-Aspartate receptor encephalitis (anti-NMDAr encephalitis), which is a relatively new disease in the neuropsychiatric panorama.

Even though it has been long established that catatonia may happen in both primary psychiatric disease and organic conditions, there are still no official guidelines on how to manage the patients whose catatonia derives from medical causes, such as anti-NMDAr encephalitis.

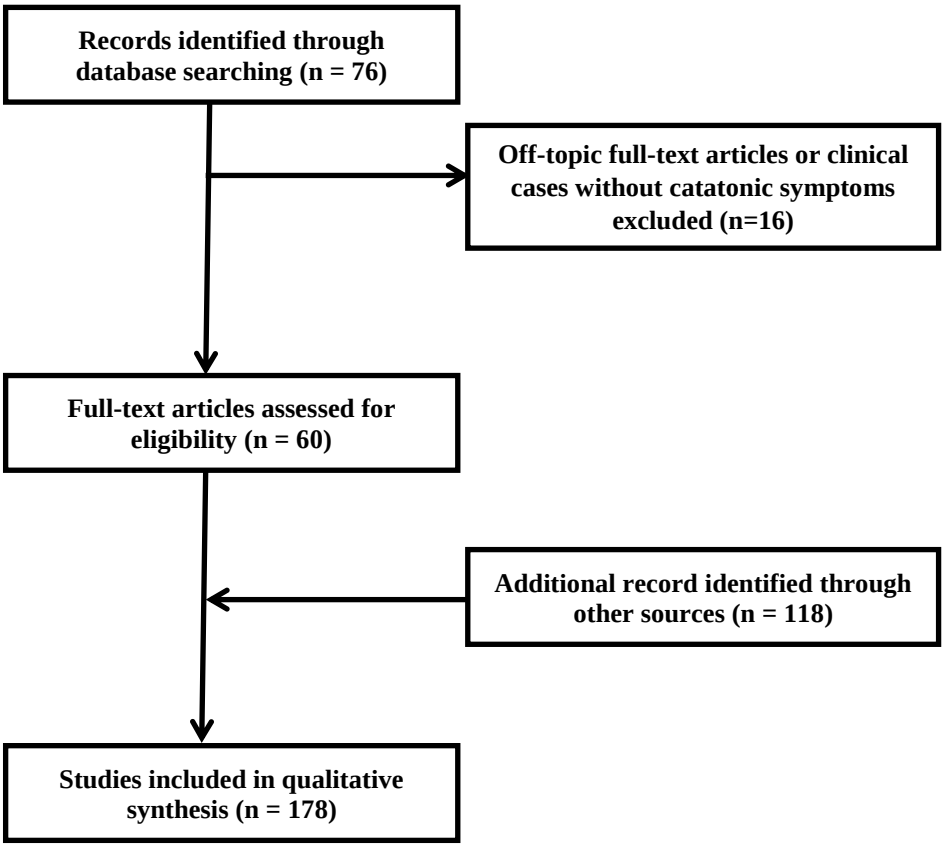
The aim of this paper is to briefly describe the history of catatonia and catatonia due to medical causes, give an overview of anti-NMDAr encephalitis, and discuss the management of catatonia secondary to this type of encephalitis by describing the clinical cases published thus far of patients presenting with this condition and catatonic symptoms.

METHODS

We performed a PubMed database search with the truncated terms "Catatoni* AND anti-NMDA receptor encephalitis". The search was last done on 19/03/2019. As the available literature about the relationship between catatonia and anti-NMDAr encephalitis is not vast, we considered any relevant studies published in English, regardless of date of publication, sample size, outcomes, comparators, or length of follow-up as potentially eligible for this article. As the potential number of available articles was small, we have also included single case reports. The research yielded 76 results from PubMed. The studies in which anti-NMDAr encephalitis considered the role of catatonia were included. Off-topic papers were excluded, as were case reports that did not feature explicitly identified catatonia. This resulted in the inclusion of 60 papers from the original PubMed research.

Due to our intention to briefly discuss catatonia, catatonia due to a medical condition and anti-NMDAr encephalitis, original data from other sources not available in our PubMed search (e.g. epidemiology numbers) but mentioned in the abovementioned papers were included in this revision and the original papers cited. This led to the inclusion of 118 extra papers. In total, 178 papers remained for inclusion in the review. Figure 1 shows the article selection process for review.

Figure 1. Article selection process for review.



CATATONIA OVERVIEW

WHAT IS CATATONIA

The term *catatonia* was first conceptualized and described by the German psychiatrist Karl Ludwig Kahlbaum in 1874,[1,2] which is why the term is also recognized by some as "Kahlbaum Syndrome".[3] It describes a complex neuropsychiatric syndrome that combines both psychic and motor symptoms, with a characteristic behavioral pattern and vegetative dysregulation – as Kaestner *et al*.[4] summarized:

- Psychomotor symptoms (e.g., catalepsy, rigidity, waxy flexibility, akinetic stupor, posturing, motor excitement and inhibition);
  - *Posturing/catalepsy* are postures that are maintained by the patient, including the mundane ones (e.g., sitting or standing for hours without reacting);[5]
  - *Rigidity* is the "maintenance of a rigid position despite efforts to be moved, exclude if cogwheeling or tremor present";[6]
  - *W*axy *flexibility* refers to the "initial resistance the patient offers during reposturing before allowing himself to be repositioned (similar to that of bending a warm candle)";[5]
  - *Stupor* refers to extreme hypoactivity and immobility, with minimal response to stimuli;[5]
  - *Motor excitement* is defined as "extreme hyperactivity and constant motor unrest, which is apparently nonpurposeful".[5]
- Imitating automatism (e.g., echolalia, echopraxia, *mitgehen, gegengreifen*);
  - *Echopraxia* and *echolalia* pertain to the mimicry of the examiner's movements and speech, respectively, by the patient;[5]
  - The german word *mitgehen* is translated as "passive obedience" and refers to the patient's act of "raising an arm in response to light pressure, despite instructions to the contrary", whilst *gegenhalten* is used as a synonym to *negativism*, which is the "motiveless (automatic rather than willful) resistance to instructions or to passive movement that is proportional to strength of the stimulus" or, in other words, is a patient with "contrary behavior/does the opposite of instruction".[5]
- Abnormal and artificial movement (e.g., grimace, mannerism, groping, parakinesia);
  - *Grimacing* is the "maintenance of odd facial expression";[5]
  - *Mannerisms* are "odd, purposeful movements (hopping or walking in tiptoes, saluting passersby, exaggerated caricatures of mundane movements)";[5]
- Stereotypies;

  - A s*tereotypy* is a "repetitive, non-goal-directed motor activity (e.g., finger-play, repeatedly touching, patting, or rubbing self)".[5]
- Rituals;
- Catatonic symptoms of speech (e.g., mutism, perseveration, verbigeration, murmur);
  - *Mutism* refers to a patient who is "verbally unresponsive or minimally responsive";[5]
  - *Perseveration* is repeated return to the same topic or persistence with the same movements;[5]
  - *Verbigeration* is the "repetition of phrases or sentences";[5]
- Negativism/positivism;
  - According to Carroll,[7] *positivism* englobes signs like automatic obedience, *mitgehen* and ambitendency, and *negativism*, as previously stated, is the resistance to instructions or attempts to move or examine the patient.
- Autonomic dysregulation (e.g., hyperthermia, dehydration, rhabdomyolysis, dysregulation of electrolytes).

As described by Carroll BT,[1] Kraepelin later classified catatonia as *dementia praecox* ("premature dementia"), but noted that it also occurred in manic-depressive illness, whereas Blueler included catatonia in his definition of schizophrenia. The German nosologist Leonhard was the first to identify catatonia as belonging to other disorders, as his definition included catatonia as a part of schizophrenia, affective psychosis, cycloid psychosis and periodic catatonia.

Although catatonia was formally associated with schizophrenia throughout the 20th century (even though it was indeed recognized outside of schizophrenia by clinicians),[8] nowadays it is well established that catatonia is an entity associated with both psychiatric and non-psychiatric conditions. In regard to psychiatric illnesses, catatonia is often found in schizophrenia, bipolar disorder and major depression,[9] while medical and neurological illnesses are among the most common causes of organic catatonia. Because of this duality in etiology, mistakes in diagnosis among patients who present with a psychiatric disturbance as the initial feature have been reported to frequently occur, and the differential diagnosis between psychiatric and non-psychiatric causes only be considered when neurological signs arise.[2] Hence, catatonia may present itself as a difficult diagnostic dilemma and a catatonic disorder due to general medical conditions must be considered in every patient with catatonic signs.[10] The fact that catatonia can lead to accelerated medical decompensation requiring rapid and effective treatment,[9] and that these patients are also often treated on hospital medical floors by internists, medical specialists, and consultation-liaison psychiatrists, only stresses the importance of remembering and excluding organic causes when receiving a catatonic patient.[11]

EPIDEMIOLOGY OF CATATONIA

The prevalence of catatonia is unknown,[11] but it has been reported to be common among psychiatric patients, with up to 10% of these inpatients may experiencing it.[12,13] However, catatonia is likely underdiagnosed by psychiatrists and other physicians, as pointed out by van der Heijden *et al.*[14] In their study, it was reported that catatonia was diagnosed clinically in only 1.3% of acute psychiatric inpatients but closer scrutiny showed that actually 18% of these patients exhibited two or more catatonic signs, highlighting the frequent underdiagnosis of catatonia in routine clinical settings.

In acute medical settings, prevalence numbers range from 1.6% [15,16] to 6.3%,[16–18] and although conditions associated with catatonia vary with the clinical setting, it is estimated that 1 in 4 patiens with catatonia has catatonia due to a general medical condition (as per criteria from the Diagnostic and Statistical Manual of Mental Disorders 5).[19]

CATATONIA SUBTYPES

The classic classification of the catatonic syndrome according to its phenotype is based on behavioral and autonomic activity, and divides it into a *withdrawn* type (also coined as *retarded-stuporous*), an *excited* type (*excited-delirious*) and a third form, called *malignant catatonia*.[4,11,19–22] The underlying cause does not appear to predict which type is expressed.[11]

- Patients with classic withdrawn-type catatonia are the ones who appear awake and watchful, but with minimal movement and spontaneous speech; frequent accompanying signs include stupor, mutism, negativism and posturing.[11] This stuporous state was the first description of catatonia (by Kahlbaum) and that may be the reason why many clinicians often have a fixed view of catatonia as a "twilight state with bizarre posturing". Eponymous include *Kahlbaum syndrome* or *delirious melancholia/depression*.[19]
- Excited-type catatonia is characterized by excessive purposeless motor activity associated with disorganized speech, disorientation, aggression and violence.[11] Eponymously called *Bell's mania*, *oneirophrenia*, *oneiroid/oneiric state* or *catatonos raptus*, *delirium acutum*, *delirious mania* per Kraepelin and *delirious catatonia*.[19]

Despite this division, it is common for patients to exhibit both forms[4] and aside from clinical vigilance related to motor consequences (e.g., preventing pressure ulcers in patients who are immobile,

or treating hyperpyrexia in psychomotor agitation), it is unclear whether there is clinical value in differentiating these phenotypical variants.[19,21]

- *Malignant* or *Lethal Catatonia* is catatonia with escalating fever and autonomic instability. It may be life-threatening because of autonomic dysregulation, hyperpyrexia, rhabdomyolysis or acute kidney injury.[19] Neuroleptic Malignant Syndrome (NMS) and Serotonin Syndrome (SS) are often considered variants of malignant catatonia. NMS is an idiosyncratic response (acute onset of fever, rigidity and autonomic signs) to dopamine receptor antagonist medications,[4] and although malignant catatonia resembles NMS in many ways, it was in fact described long before the introduction of neuroleptics.[23] SS has similar characteristics and course with malignant catatonia, but is precipitated by serotonergic medications and is typically associated with gastrointestinal symptoms, hyperreflexia or clonus.[24] Contrary to malignant catatonia or NMS (which is an idiosyncratic reaction and, thus, not dose related),[25] Serotonin Syndrome is a toxic response which is dose-dependent.[26]

CLASSIFICATION ACCORDING TO THE DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

Catatonia is a syndrome that has been progressively rediscovered and redefined throughout time. As such, its categorization under the Diagnostic and Statistical Manual of Mental Disorders (DSM) has been systematically criticized and changed. DSM III defined catatonia as a type of schizophrenia in which the main feature was marked psychomotor disturbance.[2] However, since literature reports showed that catatonia occurred most frequently in affective disorders, DSM-IV listed it for the first time as a modifier of major depression and bipolar disorder.[10]

As non-psychiatric causes began to emerge among the differential diagnosis for catatonia, the DSM-IV Organic Mental Disorders Task Force suggested that a new group of "secondary" conditions be added, which would include catatonic disorder due to a general medical condition.[10]

Nowadays, DSM-5 criteria for the diagnosis of catatonia states that at least 3 of the 12 following symptoms must be met: waxy flexibility, negativism, mutism, catalepsy, stupor, posturing, grimacing, agitation, mannerism, echolalia, echopraxia and/or stereotypy. Specifiers include catatonia associated with another mental disorder, catatonia disorder due to another medical condition and unspecified catatonia.

SCALES USED TO ASSESS CATATONIA

Due to the potential morbility and mortality associated with catatonia, the condition should be readily recognized when assessing a patient. This may be facilitated by the use of rating scales. There are various scales available to assess catatonia:

- Bush-Francis Catatonia Rating Scale (BFCRS)
- Simpson Angus Scale for Extrapyramidal Side Effects (SEPS)
- Abnormal Involuntary Movement Scale (AIMS)
- Rogers Catatonia and Schizophrenia Scales
- Global Assessment Scale (GAS)
- Modified Rogers Scale
- Clinical Global Impression (CGI)
- Bochum-German Rating Scale
- Frankfurt Scale
- Stony Brook Scale
- Pediatric Catatonia Rating Scale (PCRS)[27]

BFCRS[28] is the most widely used in research studies and case reports.[11,13] It allows for serial evaluation, but does not provide a clinical cut-off for the diagnosis of catatonia.[19] Signs included on this scale are excitement, immobility/stupor, mutism, staring, posturing/catalepsy, grimacing, stereotypy, mannerisms, verbigeration, rigidity, negativism, waxy flexibility, echolalia, echopraxia, and withdrawal. Impulsivity, automatic obedience, *mitgehen*, *gegenhalten*, ambitendency, perseveration, combativeness, and autonomic abnormalities are signs which can be also found in catatonia and are included in the scale.[11] This scale has a long version – the proper BFCRS, with 23 items rated from 0 to 3 to evaluate catatonic symptom severity –, and a shorter version – the Bush-Francis Catatonia Screening Instrument (BFCSI), with only the first 14 items, to evaluate presence or absence of catatonic symptoms, and to screen for syndrome.

Criteria require that a patient exhibit at least two of these symptoms for at least 1 hour. Symptoms not described previously on pages 6 and 7 are, as described by Dhossche *et al.*,[5] the following:

- *Starring: Fixed gaze, little or no visual scanning of environment, decreased blinking.*
- *Withdrawal: Refusal to eat, drink, or make eye contact.*

- *Impulsivity: The patient suddenly engages in inappropriate behavior (e.g., runs down the hallway, starts screaming, or takes off clothes) without provocation. Afterwards, cannot explain.*
- *Automatic obedience: Exaggerated cooperation with examiner's request, or repeated movements that are requested once.*
- *Ambitendency: Appears stuck in indecisive, hesitant motor movements.*
- *Autonomic abnormality: Abnormality of body temperature (fever), blood pressure, pulse rate, respiratory rate, inappropriate sweating.*

Although there is no single standardized approach to the assessment of catatonia and the aforementioned scales have all various limitations,[19] their use may accelerate the diagnosis in cases where catatonia may be nested within an encephalopathy, which in turn may hasten adequate treatment.[29]

TREATMENT

As with other entities, treatment aimed at the underlying etiology is always preferred, but when the cause remains unclear, symptomatic treatment is required,[13] as well as stabilization of vegetative parameters and physiotherapy.[4]

Benzodiazepines are considered first-line symptomatic treatment for catatonia (mainly lorazepam and diazepam) and electroconvulsive therapy (ECT) should be considered when benzodiazepines have failed or are only partially effective.[13,29] Both of these options have been listed as effective in both acute and chronic catatonia,[30,31] with benzodiazepines often producing reduction in symptoms within 24 hours.[32] There have been several literature reports on the excelent response and recovery produced by ECT regardless of etiology.[29,33–36] The fact that many catatonic patients respond to benzodiazepines (which are gamma-amino-butyric acid (GABA) A agonists) is a finding that supports the theory that catatonia results of decreased GABA activity.[32]

Interestingly, agents that block dopamine-2 (D2) receptors, such as typical antipsychotics, can induce catatonia in some patients (e.g., a patient described by Consoli *et al.*[37] with catatonic symptoms – and later diagnosed with anti-NMDAr encephalitis – clinically deteriorated after being prescribed loxapine, a typical antipsychotic), whereas the exact opposite seems to happen with atypical antipsychotics, such as olanzapine, with scientific literature suggesting that these may be effective in

treating catatonia. Similarly, NMDA receptor antagonists, such as ketamine and phencyclidine,[38] have been associated with the onset of catatonia, but weaker NMDA receptor antagonists, such as amantadine and memantine, have been reported to improve catatonia.[32] A theory that looks to explain these findings is that the NMDA receptor is dysfunctional[39] in catatonia in the striato-cortical pathway or cortico-cortical pathways, with NMDA hyperactivity appearing to correspond to a loss of GABA-A and dopamine activity in these regions, leading to a clinically lorazepam-resistant catatonia.[9,40] Thus, the use of NMDA antagonists to improve catatonia seems to be related to the attenuation of glutamatergic hyperactivity and possibly the simultaneous increase of GABA-A and dopamine in previously deficient areas.[9,41,42]

Catatonia is a neuropsychiatric illness that may respond to one treatment, even after failure to other standard treatments, if treated for a sufficient duration.[9] Hence, in cases refractory to both benzodiazepines and ECT, atypical antipsychotics, amantadine and memantine may constitute options worth considering.[32]

Oldham *et al.*[19] suggest the following algorithm to managing catatonia in acute medical settings:

1. *Treat the underlying cause: definitive treatment of medical catatonia is management of the underlying cause. Contributory medications should be avoided if medically feasible.*
2. *Conduct a lorazepam challenge: treatment for catatonia classically involves oral (at times via nasogastric tube), intramuscular or intravenous lorazepam 2 mg in adults or 0.5–1 mg in children or the elderly. Catatonic features should be monitored for improvement. Clinical response is defined as a 50% reduction in catatonic features as on the BFCRS. Lorazepam 2 mg can be scheduled thrice daily or increased in upward of 16 mg per day in divided doses over the following days pending clinical response.*
3. *Avoid high-potency neuroleptics. High-potency neuroleptics are not effective for catatonia. They can cause catatonic-like (i.e. extrapyramidal) side effects and may potentiate NMS. Recent reports suggest that atypical antipsychotics may improve non-malignant catatonia but should be used with caution as an adjunct to a benzodiazepine or other catatonia-specific intervention. It is unclear whether high-potency neuroleptics for the management of catatonic excitement can be used safely as an adjunct to catatonia-specific treatment.*
4. *Ensure appropriate supportive measures: guidelines on the supportive management have been reviewed previously. The first three apply to both excited and stuporous catatonia; the remaining five are exclusive to stuporous variants.*
    a. *Reverse hyperthermia.*

   b. *Hydrate to prevent acute kidney injury.*
   c. *Maintain adequate nutrition.*
   d. *Monitor oxygenation closely.*
   e. *Provide prophylaxis for deep vein thrombosis or pulmonary embolism.*
   f. *Prevent pressure ulcers.*
   g. *Prevent muscle contractures.*
   h. *Mitigate against aspiration pneumonia.*
5. *Consider a NMDA receptor antagonist or topiramate: Small case series support the use of the NMDA receptor antagonists amantadine or memantine or the anticonvulsant topiramate in catatonia unresponsive to lorazepam. Despite the absence of formal guidelines, agents other than lorazepam may be considered within 1–3 days of a negative lorazepam trial.*
6. *Initiate ECT: Nearly 90% of catatonia respond to ECT including cases of malignant catatonia. In cases of malignant catatonia (i.e. autonomic instability, hyperpyrexia, rhabdomyolysis), ECT should be considered as an emergent intervention. Where patients refuse to eat and are unable to provide self-care, ECT should be considered urgently. ECT should also be considered when only partial response is obtained from medication trials.*

CATATONIA SECONDARY TO ORGANIC CAUSES

Medical catatonias can developed secondarily to an illness or exposure to a substance (or both simultaneously), although they more often develop in patients with other psychiatric and medical risk factors.[10] Identification of the catatonic syndrome must be made while simultaneously determining its cause.[11] Some examples of the plethora of specific states that can manifest themselves through behavioral symptoms include central nervous system (CNS) tumors (with symptoms determined by the location and properties of the tumor), thyroid disease (both hyper and hypothyroidism), Wernicke's encephalopathy, Nonconvulsive *Status Epilepticus* and encephalitis;[43] cases pertaining to catatonia secondary to multiple sclerosis, uremia and metabolic ketoacidosis have also been reported.[11]

There seems to be no difference in the expression of catatonic symptoms in patients with underlying psychiatric or medical causes.[11]

When first assessing a patient with behavioral symptoms, certain features can suggest a medical etiology:[43–47]

- Any atypical feature for a specific psychiatric diagnosis;

- A behavioral symptom disproportionately severe to that expected of the psychiatric syndrome alone;
- Late age of onset of a new behavioral symptom;
- Absence of a personal history or family history of psychiatric illness;
- Sudden onset of psychosis or delirium;
- Intoxication with, or withdrawal from, a drug or toxin with psychiatric manifestations (e.g., delirium or psychosis), or the presence of a characteristic toxidrome even in the absence of a specific history;
- Systemic disease, evidence of increased intracranial pressure, nonauditory hallucinations (visual hallucinations, distortions, and illusions may be good discriminators of medically induced psychiatric disorders);
- Prescription drugs with potential psychoactive properties such as digoxin (particularly in the elderly), or any centrally acting drug;
- A temporal relationship between the onset, exacerbation, or remission of psychiatric symptoms and the medical condition;
- The occurrence of autonomic dysfunction with a history of good premorbid function;
- Treatment resistance.

If one or more vital signs or abnormal findings on physical examination (e.g., fever, sensory inattention) are present, the patient should be regarded as having a medical illness; a thorough neurologic examination is also required, as is a mental status examination. The mental status examination can sometimes help to distinguish medical from psychiatric disorders since abnormal functioning, particularly that regarding orientation, memory or level of consciousness are uncommon in psychiatric disorders.[43]

As will be further discussed, encephalitis is important in the differential diagnosis of catatonic states,[10] as several cases of encephalitis (of various etiologies) presenting as catatonia have been described.[2]

EPIDEMIOLOGY

Catatonia due to a medical condition is believed to be common,[11] although its frequency may vary with the clinical setting.[10] Studies reporting on its epidemiology are diverse. According to a paper by

Daniels *et al.*,[11] the frequency of catatonia due to a general medical condition in psychiatric units was measured at 20%–25%, based on three prospective prevalence studies conducted after 1985.[28,48,49]

The majority of medical catatonias appears to be due to neurological disease.[19,50] In a systematic review on the relationship between catatonia and delirium, Oldham *et al.*[19] described other reviews that reported on epidemiologic data of catatonia due to medical causes: a systematic review[10] of medical catatonia cases found that roughly 70% were due to a neurological condition, 30% of which were associated with structural CNS disease, 25% with encephalitis or other CNS infection, and 10% with seizure disorder. Likewise, a 20-year retrospective Mayo Clinic chart review[51] identified 95 in-house cases of catatonia per DSM-IV-TR criteria, 20 of whom had medical catatonia and among those, 70% had neurological illness: the most common etiologic diagnosis was encephalitis, with 6 patients who suffered from it, 4 from major neurocognitive disorder, 3 from seizure disorders and 1 from CNS metastases. Moreover, a 2008 review[52] of pediatric medical catatonias identified 26 cases related to medical conditions and 12 related to medications or toxins. Among the 26 medical catatonias, 10 were related to neurological conditions, 6 genetic conditions (all known to affect brain development), and 4 viral encephalitides — this sum up to 77% of causes having cerebral involvement.

INVESTIGATION

Various authors[10,22] have suggested that the differential diagnosis of catatonia due to a medical condition should be divided into simple categories as neurologic, substance-induced, metabolic, infective and endocrine disorders. Subcategories as encephalitis, seizure disorders and others, should be made, as they allow for a more focused study and practical clinical application.

Lumbar puncture and cerebrospinal fluid (CSF) studies are recommended when investigating a patient with catatonia of unclear etiology.[10] Lumbar puncture was found to be test most likely to affect acute management.[51]

Regarding encephalitis as the underlying cause, catatonia may be difficult to assess in the context of encephalopathy and this can easily lead to the use of neuroleptics. As previously discussed, the use of catatonia rating scales is encouraged, as to facilitate earlier detection, and neuroleptics should be avoided in patients with catatonic features (and discontinued if malignant catatonia is suspected).[29]

When associated with encephalitis, catatonia does not seem to be correlated with the inciting pathophysiology (which may include infectious, paraneoplastic, and inflammatory mechanisms).[51,53]

ENCEPHALITIS OVERVIEW

As mentioned previously, a high percentage of secondary catatonia is caused by neurological disorders, specifically encephalitis. Encephalitis is an acute inflammatory process of the brain parenchyma that generally presents with an altered level of consciousness, disorientation or behavioral and speech disturbance[43,54] and its clinical findings depend on the location and extent of the particular regions of the brain that are affected.[43,55–57] The condition may be life threatening and as such requires prompt diagnosis and adequate treatment. Etiologies comprise a range of inflammatory disorders, including paraneoplastic, autoimmune and infectious causes.[58,59] Across the range of etiologies, common symptoms of encephalitis may include headache, confusion, altered level of consciousness, memory disturbances, seizures, and hallucinations. Particular symptom clusters may lead the clinician to consider one etiology over another.[59]

Studies[60,61] have led to the characterization of autoimmune encephalitis into two broad categories:[62]

- Those associated with antibodies to intracellular neuronal antigens (i.e., antigens located in the nucleus or cytoplasm, such as Hu, Yo and Ma2). The more frequently encountered intracellular autoantigens are Hu and Ma2, with CV2/CRMP5 and amphiphysin present less often. This type of immune-mediated encephalitis is more often associated with neoplasms. Since the target epitopes in these disorders are intracellular, and therefore the antibodies have only limited accessibility, it has been suggested that many of these antibodies are not pathogenic, but rather reflect a cytotoxic T-cell mediated immune response.[63] These encephalitides often show limited response to treatment.
- Those associated with antibodies to cell membrane antigens, such as NMDA receptors,[64] voltage-gated potassium channels,[65] alpha-amino 3-hydroxy 5-methyl 4-isoxazolepropionic acid (AMPA) receptors,[66] the GABA-B receptor,[67] the glycine receptor (GlyR),[68] and the metabotropic glutamate receptor 5 (mGluR5).[69] These encephalitides are less frequently associated with cancer, have an antibody-mediated pathogenesis, and tend to respond to immunotherapy.[70]

ANTI-NMDA RECEPTOR ENCEPHALITIS OVERVIEW

All cases discussed in the following sections and that report the coexistence of anti-NMDAr encephalitis and catatonia are summarized on Table 1, page 43.

WHAT IS ANTI-NMDA RECEPTOR ENCEPHALITIS

NMDA receptors are heteromers of NR1 and NR2 subunits (A, B, C or D) that bind glycine and glutamate, respectively,[71] and compose ligand-gated cation channels that play an important role in synaptic plasticity[72] and which seem to be involved in the physiopathology of neuropsychiatric disorders.[73] In order for the NMDA receptor to be functional, both glycine and glutamate must bind to the heteromers.[37]

Anti-NMDAr encephalitis is a type of encephalitis characterized by the presence of antibodies against the NMDA receptor, more precisely against the NR1/NR2 heteromers of the receptor. These antibodies were first discovered in 2007 by Dalmau *et al.*,[74] which coined the term "anti-NMDA receptor encephalitis" in a patient with an ovarian teratoma. In 2008, the syndrome was fully described in a case series of 100 patients.[64]

Although these antibodies were only described in 2007, the association between subacute encephalitis and a distant tumor was first reported by Brierley *et al*. in 1960[75] and the clinical syndrome of a paraneoplastic neuropsychiatric disorder associated with ovarian teratoma was primarily described in 2005 by Vitaliani *et al*.[37,76]

In adults, the disorder is often associated with neural tissue within a tumor which can express NMDA receptors, inducing antibody production. The generated autoantibodies then bind to host NMDA receptors located in the brain, leading to reversible receptor internalization by autophagy and consequent marked loss of such surface NMDA receptors and NMDA receptor clusters in postsynaptic dendrites.[62,77–79] The classically and most frequently described associated tumors are ovarian teratomas in women and testicular tumors in men,[37,80] but there are literature reports of other forms of neoplasms, such as small cell lung cancer and neuroblastomas.[81,82]

The antibodies are detected in the CSF and/or serum of the patient and tend to disappear with clinical improvement, suggesting their pathogenic role.[83]

Although initial presentation can be variable, the natural history of the disease has now been clearly described and can be reasonably predicted. The disease evolves in stages, ultimately culminating in either recovery (limited to full) or death:

- Approximately 70%[84] of patients report the occurrence of a prodromal phase, which consists of a brief nonspecific viral-like episode with fever, malaise, headache, fatigue, vomiting, diarrhea and/or upper respiratory tract symptoms.[77]

- This stage is followed by an acute phase that includes neuropsychiatric symptoms such as agitation, psychotic symptoms (i.e., delusions or hallucinations), behavioral changes, generalized or partial seizures and progressive unresponsiveness, shortly followed by abnormal movements (e.g., dyskinesia), autonomic instability (e.g. paroxysmal hypertension and sinus tachycardia, hypo- or hyperthermia, bradycardia, hypotension, gastrointestinal dysmotility, and sialorrhea)[85] and hypoventilation that may require ventilation assistance and intensive care.[37,62] It is in this phase that many patients present to psychiatrists or are admitted to psychiatric units with a diagnosis of acute psychosis or schizophrenia.[62]
    - Psychiatric symptoms consist of anxiety, mood dysregulation, or depression progressing to severe behavioral and personality disturbance, delusional or disorganized thinking, paranoid ideation, and hallucinations.[62]
    - In the unresponsive state, affected individuals have their eyes open but are unresponsive to visual threats. These patients are often mute, or they only mumble unintelligible words. Muscle tone is often increased, and catatonia may happen with possible dystonic and/or cataleptic postures.[62]
    - Dyskinesias tend to start in the face and/or mouth and include orofacial dyskinesia (described as kidding, chewing, tongue thrusting, lip smacking, facial grimacing, frowning, and fish- or rabbit-like movements). Although associated with rhythmic abdominal contractions or complex movements of the extremities, these orofacial dyskinesias do not have epileptic correlates on the electroencephalogram (EEG).[62] Other movement disorders include complex and stereotyped movements as pelvic thrusting, 'floating' of the hands into the air, pseudoplaying piano motions and writhing movements of the extremities. Limb movements can be independent or synchronous, at times mimicking epileptic seizures. The movements persist despite declining consciousness, often to the point of self-injury. In severe stages, there may be episodic opisthotonus, dystonic posturing and oculogyric crises, which are associated with tachycardia and hypertension, reminiscent of autonomic storming.[81]
    - Hypoventilation of a central origin may be missed until extubation is attempted.[62]
    - Autonomic instability is not uncommon and is evidenced by blood pressure and temperature fluctuations, tachycardia, bradycardia, and even cardiac pauses.[62]
    - The speech disturbance in anti-NMDAr encephalitis manifests as a progressive language disintegration, with the symptomatic spectrum ranging from reduction of verbal output and echolalia (frequently accompanied by echopraxia) to frank mutism.[81]

- Insomnia is often prominent at presentation, and less frequently in the stages of recovery. Patients may not sleep for days regardless of trials of multiple sedating medications. When sleep does occur, sleep–wake cycles are disturbed and patients wake frequently throughout the night. During recovery patients may have hypersomnia and other symptoms of hypothalamic dysfunction.[81]

While patients might present with the complex neurological deterioration described above, milder or incomplete forms of anti-NMDAr encephalitis have been observed in a subset of patients, with predominant or isolated psychiatric symptoms.[77,86] A 2018 review of the psychiatric phenotypes seen in anti-NMDAr encephalitis by Sarkis *et al.*,[87] found that 77% of patients with this type of encephalitis presented initially with psychiatric symptoms and of those, catatonia was present in 42% of adult patients and 35% of children. Interestingly, they also found that in many cases, although the signs and symptoms of catatonia were clearly described, the authors didn't explicitly identify catatonia.

Hughes *et al.*[78] hypothesized that the profile of psychiatric symptoms could be dependent on the intensity of the antibodies effects on the density of NMDA receptors, similar to what has been previously described regarding the effects of different doses of NMDA antagonists: low doses of ketamine hydrochloride and phencyclidine cause psychosis, anxiety, agitation, memory disturbance, decreased responsiveness to pain and speech reduction, while higher doses were associated with dissociative anesthesia, profound unresponsiveness with catatonic features, orofacial and limb dyskinesias, autonomic instability and seizures.[88–91] Patients with isolated psychiatric symptoms may have prolonged periods without treatment but not necessarily progress to more severe disease because of that.[86] In a case described by Hermans *et al.*,[92] a 25-year-old woman presenting with psychiatric symptoms, and later progressing to catatonia and autonomic instability, went 74 days without the correct diagnosis of anti-NMDAr encephalitis and yet had a good prognosis once adequate treatment was initiated, having returned to her premorbid level. Heekin *et al.*[93] presented the case of a woman who was followed up for over 14 years for the treatment of multiple neuropsychiatric symptoms. Initially, she presented with paresthesias, memory loss, and manic symptoms; nine years later, she was admitted with left sided numbness, left eyelid droop, and word finding difficulties. She was conservatively managed and presented with spontaneously resolved symptoms at a follow-up visit five months later. Five years after that, she presented with manic symptoms, hallucinations, and memory impairment, having subsequently developed catatonic symptoms and seizures during her stay at the hospital. She was found to be positive for anti-NMDAr antibodies and her symptoms responded well to immunotherapy. The authors hypothesize that if this patient's episodes "are in fact attributable to pathogenic anti-NMDA receptor antibodies, this would constitute an extensive illustration of the

natural history of the disease in a patient not initially treated with immunotherapy or tumor removal, characterized by relapsing and remitting symptoms subsequently progressing to florid disease with seizures, dyskinesias, and autonomic dysfunction, ultimately requiring intubation and mechanical ventilation".

An interesting feature in anti-NMDAr encephalitis is that recovery follows a sequential multistage process that develops in the opposite direction to that of symptom presentation.[81]

In young children, the syndrome is similar, but the presenting symptoms may be different. Studies have shown that children tend to have neurological symptoms more frequently (such as abnormal behavior, seizures and movement disorders),[90] as opposed to psychiatric ones. They also appear to have a higher incidence of movement disorders, with numbers of children noted to have a movement disorder ranging from 60%[94] to 90%,[95,96] which includes unilateral dystonia, speech disturbances (reduced speech, mutism, echolalia, or perseveration),[80,97] *status epilepticus*[81] and gait disturbances.[98] Granata *et al.*[99] compared the movement disorders in children and teenagers (>12 years of age) with anti-NMDAr encephalitis and found that catatonic symptoms were much more prevalent in adolescents than in children, as other studies[100] had shown before. In children, especially those under 12 years of age, behavioral changes may present themselves with increased temper tantrums, hyperactivity, or irritability as opposed to frank psychosis.[90]

Such as psychiatric symptoms, autonomic dysfunction that is common in adults occurs less frequently in children. Although more than 42% of adults develop hypoventilation, this occurred in only 16% of one series of children.[90] When dysautomy does happen in children, it usually manifests as urinary incontinence and episodes of tachycardia, hypertension, or hyperthermia, with severe cardiac dysrhythmia and other clinically significant cardiac pauses being less frequent when compared to adults.[80,101]

WHY IS IT IMPORTANT

Recognizing anti-NMDAr encephalitis as a possible cause for catatonic presenting patients is important for several reasons:

- First, many patients may initially present with psychiatric symptoms and catatonic features,[37,102] and can be misdiagnosed with a primary psychiatric disorder, with the definite diagnosis and adequate treatment being delayed. This was the case of a 25-year-old female patient described by Hermans *et al.*[92] (and previously mentioned in this paper), who

presented primarily with psychiatric symptoms was misdiagnosed and treated as a first psychotic episode within a primary psychiatric disorder. Despite having rapidly deteriorated to catatonia followed by autonomic instability, the diagnosis was still delayed by 74 days. Likewise, Jones *et al.*[84] described the case of a 17-year-old girl who presented with altered mental status, seizures, catatonia and autonomic disturbances, who was submitted to over 4 weeks of evaluation and work-up by internal medicine, neurology, infectious disease, and psychiatric services at two different facilities before an accurate diagnosis was made and a sustainable treatment modality initiated. Both cases highlight the importance of the need for greater recognition of this autoimmune disorder. Then there are cases of patients who may have a history of catatonic episodes throughout several years, who were symptomatically treated, but remained with a diagnosis of unclear etiology, like the case described by Tsutsui *et al.*,[103] whose patient was admitted for catatonic symptoms and treated with steroids and antipsychotics and discharged, and only later was diagnosed with anti-NMDAr encephalitis. This patient is interesting because 3 years before he had also presented with an episode of catatonia of unclear etiology, and one could question whether this was also due to the presence of anti-NMDAr antibodies.

- Secondly, these patients frequently have an increased mortality and morbidity risk if not treated promptly, frequently requiring intensive care assistance.[84] Both anti-NMDAr encephalitis and catatonia have effective treatment available[104] and given the possibility of severe neurological sequalae and death, the importance of searching for a medical condition in a catatonic syndrome is related to treating appropriately and avoiding such outcomes.[37,105] Early identification and intervention can shorten the duration of intensive care admission and ventilation, improve the outcome, and protect against relapse.[96,106,107]

EPIDEMIOLOGY

Since 2007, when anti-NMDAr antibodies were first described, various case reports of anti-NMDAr encephalitis have been published, suggesting that the illness is not rare.[37,108–112] The exact incidence of anti-NMDAr encephalitis is unknown, but it seems to be more frequent than any other known paraneoplastic encephalitis[37,77] and even more frequent than any specific viral etiology in young patients, as reported by the California Encephalitis Project.[70,113] In children and adolescents, anti-NMDAr encephalitis has become a leading cause of autoimmune encephalitis, with 40% of patients being younger than 18 years of age.[77]

Anti-NMDAr encephalitis was initially described as typically occurring in young women,[104] with papers suggesting up to 80%[37] of patients being females between the ages of 14 and 44.[58] However, cases in male patients – both children and adults – began being increasingly and repeatedly described, so as to the extent that the disease is now described as affecting children and young adults[37] with a median age of onset at 23 years, although it ranges from 3 to 76 years.[64,114,115]

The frequency of tumors varies according to age, sex and ethnicity:[37,64] its presence has been reported to be more frequent in women who are older than 18 years and who are black,[37,77] and most likely in adolescents and adult females,[94] while children and males have a lower incidence of tumors[62,81] (with a tumor being found in approximately 6% of girls younger than 12 years and rarely in boys).[94,95] In a substantial number of patients, no primary tumor is found and the trigger of the immune response is unknown. According to a literature analysis of cases of anti-NMDAr encephalitis by Kruse *et al.*,[59] only 38% of patients have an underlying neoplasm; neither case described by the authors had an underlying malignancy.

Although rare, cases to have occurred during pregnancy have been reported, as well as in the post-partum setting.[116,117]

As previously stated, delay in diagnosis is not uncommon, with a median time from symptom presentation to initial signs of improvement at around 6 weeks.[80,118]

Mortality rates of anti-NMDAr encephalitis have been reported at 8–10%.[115]

DIFFERENTIAL DIAGNOSIS

Although the constellation of symptoms in anti-NMDAr encephalitis is characteristic, the disease evolves in stages and so certain presentations at certain stages of the disorder may suggest alternative diagnoses, and the list may be vast.

The most frequently considered disorders in the differential diagnosis of anti-NMDAr encephalitis are toxic and metabolic disorders, infectious encephalitis, other causes of autoimmune encephalitis and primary psychiatric diseases.[104,108] Kiani *et al.*[119] described the case of a 32-year-old woman with a diagnosis of mild intellectual disability, autism and Larsen's syndrome, whose catatonia presented after the initiation of antipsychotics and thus the first diagnosis considered was NMS . However, given the multitude of psychiatric symptoms she also presented with, a diagnosis of functional catatonia was found to be most appropriate and the diagnosis of anti-NMDAr encephalitis was later established.

- Toxic causes include over-the-counter or illicit drugs (e.g., phencyclidine)[38], as well as carbon monoxide, methanol, and cyanide. Ketamine is a drug that affects the NMDA receptor and thus produces similar symptoms to anti-NMDAr encephalitis.[81]
- Porphyria, mitochondrial disorders, and disorders of amino or organic acid metabolism should also be excluded.[62]
- Infectious causes include viral (herpes simplex virus (HSV), human herpes virus-6 (HHV-6), enteroviruses, arboviruses, mumps, measles, varicella zoster (VZV), cytomegalovirus (CMV), rubella, influenza, human immunodeficiency viruses (HIV), rabies virus), bacterial (*Tropheryma whipplei*, *Mycoplasma pneumonia*, *Bartonella henselae*, *Listeria monocytogenes*, *Borrelia burgdorferi*, *Treponema pallidum*), parasitic (*Toxoplasma gondii*, malaria, primary amoebic meningoencephalitis) and fungal (*Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides*).[59] Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS) is also a differential diagnosis to be taken into account in children.[81]
    - The most frequent viral causes include HSV HHV-6; VZV and CMV, although frequently included in CSF screening testing, are viruses that are rarely responsible for viral encephalitis.[62,108]
- Other autoimmune etiologies for encephalitis include those involving the previously mentioned classic paraneoplastic antigens or cell membrane antigens (with antibodies to Hu, Ma2, AMPA receptors, *etc.*), acute disseminated encephalomyelitis (ADEM),[59] systemic lupus erythematosus cerebritis, antiphospholipid antibody syndrome, Sjögren's syndrome, encephalopathy associated with Hashimoto's thyroiditis, and angiitis (primary or systemic).[62]
- Primary psychotic disorders, schizophreniform disorder and even schizophrenia, mood dysregulation disorders, disorders of impulse control, and sleep disorders are also often considered within the list of primary psychiatric disorders.[62] It's not uncommon that patients, particularly adults, are initially diagnosed with new onset psychosis, when antibodies have not yet been identified and the disease has not progressed in a temporal continuum so as to provide a pattern of recognition. These patients are often treated initially with medications like haloperidol, and when anti-NMDAr encephalitis expected signs and symptoms arise (like rigidity and autonomic instability), sometimes with accompanying elevation of muscle enzymes,[62] they are diagnosed with NMS.[81] Some features that may help to clinically distinguish patients with anti-NMDAr encephalitis from those with a true psychiatric disorder include anterograde amnesia (impairment of short-term amnesia), which is usually present in

patients with NMDAr antibody-associated encephalitis but frequently overshadowed by the neuropsychiatric symptoms of the disease, the development of dystonia, seizures, decreased level of consciousness and central hypoventilation requiring mechanical ventilation, all happening in this form of encephalitis and absent in primary psychiatric disease.[104] Verfaille *et al.*[120] described the case of an 18-year-old who presented with acute psychosis who later progressed to a rapidly evolving neuropsychiatric syndrome, characterized by severe motoric dysfunction (episodes of catatonia and agitation, orofacial dyskinesia, and dystonic posturing with head deviation) and autonomic instability requiring intubation, and was later found to have highly positive anti-NMDA receptor antibodies. In 2018, Warren *et al.*[121] published a systematic review of the psychiatric symptoms of anti-NMDAr encephalitis looking for symptoms able to differentiate the presentation from a primary psychiatric disorder, and found that catatonia, especially when fluctuating (changing from severe agitation to withdrawal and mutism repeatedly), is a key feature which may indicate this type of encephalitis and may be a potentially useful diagnostic tool, yet has been minimally highlighted in medical literature.

DIAGNOSIS

Definitive diagnosis is established by demonstrating antibodies to the NR1 subunit of the NMDAr in serum or CSF of the patients with a suggestive clinical context.[122] According to Dalmau *et al.*,[64,77] IgG NR1a antibodies in serum and CSF represent a specific immune profile for NMDAr encephalitis. Steiner *et al.*[91] suggested that the clinical manifestation of the condition may vary on the kind of subunit blockade caused by the antibodies. Serum and CSF antibody titers appear to be correlated with the course of the disease[81] and possibly with the existence of associated tumors, with higher titres of antibodies often being associated with their presence.[123]

Most patients have intrathecal synthesis of anti-NMDAr antibodies,[59,77] so detection of antibodies in the CSF is more sensitive and often presents higher titers[64,78] than detection in serum, with the latter not having detectable titers at all in some cases.[104] In an observational cohort study by Titulaer *et al.*,[95] of the 250 patients diagnosed with anti-NMDAr encephalitis, 100% had anti-NMDAr detected in the CSF, but only 85% had anti-NMDAr antibodies detected in the serum. Serum and CSF antibodies that reacted with both NR1/NR2 heteromers (NR2a-2b) of NMDA receptors are considered to be highly specific for the disorder.[104] Commercially available paraneoplastic antibody tests do not detect anti-NMDAr antibodies and so, until this test becomes commercially available, serum and CSF should be sent to a research laboratory that carries out analysis of these antibodies.[104]

Steiner *et al.*[91] looked to compare the specificity and prevalence of NMDAr antibodies in schizophrenia (DSM-IV criteria) with those of other psychiatric diagnoses and to determine whether antibody subtypes characterize overlap with and distinction from those in NMDA-R encephalitis. Their findings suggest that the "repertoire of antibody classes (IgA, IgG, and IgM) and epitope targets (NR1a alone vs NR1a/NR2b) is wider in patients with the psychiatric diagnoses of schizophrenia, major depression, or borderline personality disorder than in patients with anti-NMDAr encephalitis (specific IgG NR1a antibodies in serum and CSF)."

Although it's been initially reported that no false positive test was found in approximately 400 controls studied with diverse neurological disorders (J. Dalmau, pers. comm., 2008),[104] recent reports have come to contradict this finding: besides previous papers stating anti-NMDAr seropositivity in patients later diagnosed with prion disease,[124] Zandi *et al.*[123] showed that some patients with low positive serum results were later found to have neurodegenerative disorders instead. These findings raise the question of whether the sole identification of anti-NMDAr antibodies is enough for the confirmation of anti-NMDAr encephalitis. Moreover, the authors also showed that even the method through which the antibodies are detected and measured has some implications: they found that the use of live cell assays (as opposed to fixed-cell assays) resulted in antibody levels that were always higher in the serum than in the CSF, and that the latter could inclusively not always be positive in patients with lower serum levels. This data seems to go against the initial description that antibody detection in the CSF appeared to be more sensible than detection in the serum and that CSF positivity could be associated with seronegativity. It seems reasonable, however, to remember that NMDA receptors are also present outside the brain (in organs like the heart, kidney and lungs)[125,126] and that, as noted by Dalmau *et al.*[77] back in 2011, there is an immune response that is initially triggered systemically by a tumor or other unknown causes and is reactivated and expanded in the CNS. Hence, the contribution of peripheral tissues to autoantibody production warrants further investigation.[91]

On the opposite side of the spectrum, an initial negative test for anti-NMDAr antibodies in the CSF or serum does not exclude a diagnosis, and a follow-up test should be done. This may happen because antibody levels may not develop fast enough despite the presence of a clinically active condition. A case described by Gulyayeva *et al.*[75] reported on the detection of antibodies against NMDA receptors in the serum and CSF only in the second set specimens (the first set had come back negative) in a 22-year-old woman.

OTHER INVESTIGATIONS

Anti-NMDAr encephalitis is classically described as being associated with a tumor. As such, when the diagnosis is confirmed, a comprehensive search for a neoplasm should be conducted simultaneously to the start of adequate treatment.

- As previously described, most female patients have an ovarian teratoma, which often is a benign or mature dermoid cyst. Investigations include a vaginal ultrasound and pelvic computed tomography (CT). Magnetic resonance imaging (MRI) has also been used as it seems to have higher sensibility in the detection of early, small ovarian tumors.[81] Recurrent and bilateral neoplasms can occur and the teratoma may be located at a different site.[104,127] As 70% of the tumors are benign, positron emission tomography (PET) can be negative.[76]
- Regarding testicular teratomas in male patients, ultrasound of the pelvis is an appropriate initial screen measure.[81]

Approximately 30% of patients have no detectable tumor (J. Dalmau, pers. comm., 2008)[104] and it's unclear whether these patients have an underlying tumor that will manifest months or years later. Iizuka *et al.*[128] has reported on teratomas found up 7 years after onset of the encephalitis. These findings highlight the need for regular follow-up visits.[58]

Regarding other exams:

- For patients with anti-NMDAr encephalitis, brain MRI is frequently normal (up to half of affected patients[74]) or show only minor and non-specific signs, such as T2 or fluid attenuated inversion recovery (FLAIR) signal hyperintensity in various areas of the brain, including the hippocampus, cerebellar or cerebral cortex, basal ganglia, brainstem, and spinal cord,[64,70,74,96] sometimes with subtle, transient cortical or meningeal contrast enhancement.[81] However, although infrequently, the MRI may show intense and extensive FLAIR abnormalities.[81]
- Patients' CSF may show pleocytosis (with white blood cell counts often elevated but usually lower than 200 cells/mm^3)[81] and an elevated protein concentration. Initially, lymphocytosis and sparse oligoclonal bands are present, but with evolving disease, lymphocytosis decreases and oligoclonal bands become more prominent.[120,129] Determination of immunoglobulin (IgG) index and oligoclonal bands is useful, particularly in cases with normal cell count and protein concentration because these can be abnormal in such cases.[81]
- EEG is abnormal in 90% of patients with anti-NMDAr encephalitis[95] but this is not diagnostic.[70] Hence, EEG studies are not particularly helpful in making a specific diagnosis of this condition.

However, EEG is helpful in differentiating between psychiatric and encephalitic etiologies of psychiatric and behavioral manifestations, because most patients with encephalitis will have EEG abnormalities. Patients with anti-NMDAr encephalitis most frequently have an EEG that exhibits non-specific, slow and disorganized activity[37] and occasionally epileptic activity.[59,120] Seizures occur more often at early stages of the disease, but in catatonia slow continuous rhythmic activity may happen in the delta–theta range. However, this EEG activity does not correlate with abnormal movements and does not respond to anti-epileptics.[81] Recently, a unique EEG pattern described as "extreme delta brush", identified in 30% of adult patients with anti-NDMAR encephalitis, has been described as possibly characteristic of the disorder and associated with more prolonged hospitalization.[70,130] EEG abnormalities in anti-NMDAr encephalitis appear to resolve with clinical improvement.[93,96,130]

TREATMENT & PROGNOSIS

The primary objective of therapy is to reduce or eliminate anti-NMDAr antibody levels, with eradication of associated malignancy or suppression of the immune reaction. Thus, the optimal management of anti-NMDAr encephalitis is tumor resection and immunotherapy. When instituted promptly, these interventions have been shown to decrease morbidity and mortality and reduce the risk of irreversible neuronal damage, with evidence suggesting that early use of immunosuppressants may lead to a more rapid recovery and decreased morbidity.[62,64,80,81,96,131] Intensive Care Unit (ICU) care for ventilatory support, seizures and autonomic instability can delay tumor removal but it's been shown that in some patients tumor removal results in significant neurological improvement within days to several weeks.[74,104]

Management of psychiatric symptoms (which includes catatonia) is, therefore, primarily based on etiologic treatment. There are, however, reports of patients who presented with intermittent catatonia and who improved without immunotherapy, as described in the paper published by Yoshimura *et al.*,[132] whose two patients were managed with antipsychotics and benzodiazepines.

There are no established guidelines for the treatment of anti-NMDAr encephalitis, but Dalmau and colleagues[77] proposed an algorithmic strategy to guide treatment based on an extensive literature review (400 patients over a 3-year period). In summary, their proposed pharmacological treatment approach is the following:

- The first-line of immunotherapy consists of corticosteroids, intravenous immunoglobulins (IVIg) and plasma exchange (alone or in combination):[120]
    - Methylprednisolone 1 g/day for 5 days;
    - IVIg 0.4 g/kg/day for 5 days.

The authors have shown that this first-line of treatment may result in partial neurological improvement or stabilization, with titers being effectively reduced by these immunomodulatory treatments.[133]

Voice *et al.*[134] described the case of a 17-year-old with anti-NMDAr encephalitis with catatonic symptoms which resolved when all three first-line measures were combined after tumor resection (left ovarian teratoma), as was the case with the 19-year-old woman treated by Gulyayeva *et al.*[75] (also an ovarian teratoma). Chatterjee *et al.*[102] described a patient who improved, catatonic symptoms included, with methylprednisolone and plasmapheresis, as did the patient described by Mythri *et al.*,[135] with immunotherapy only.

In children, plasma exchange is less often used because of the frequent need for central line placement. There is a subset of patients who remain symptomatic despite these therapies. In some of these patients, serum and CSF antibodies remain high, suggesting that additional courses of IVIg, methylprednisolone, or plasmapheresis may be helpful.[81]

Overall, immunotherapy and tumor removal (when appropriate) result in marked improvement or full recovery of 75% of the patients.[64] Patients who have a tumor detected and removed within 4 months of onset have a more complete and fast recovery when compared to those without teratoma.[81]

In refractory cases (patients who do not respond to first-line therapy, which comprise approximately 50% of NMDAr encephalitis patients),[95] particularly those with no response after 10 days, severe symptoms at 1 month, delayed diagnosis or in the absence of a tumor, additional treatment may be necessary with second-line immunotherapy:[37,81]

- Second-line immunotherapy is composed of rituximab, cyclophosphamide or both.
    - Rituximab is given at a dose of 375 mg/m^2/week for 4 weeks (in adults);
    - Cyclophosphamide at a dose of 750 mg/m^2;
    - This treatment is discontinued when patients have substantial clinical recovery. Irani *et al.*[136] suggest that pulsed intravenous methylprednisolone treatment should be followed by oral prednisolone administration, which is tapered over a period of 6 to 12 months after hospital discharge.[120]

- The immunosuppressive agent mycophenolate mofetil is also considered as second-line therapy, being recommended for patients with non-paraneoplastic encephalitis for a minimum of 1 year.[137]
- The use of azathioprine[58] (e.g. a published by Kuppuswamy *et al.*[138]), alemtuzumab[139] and bortezomib[140] has also been described in the neurological literature.

In 2009 Parratt *et al.*[112] published a case regarding a woman whose symptoms did not respond to IVIg, methylprednisolone, plasmapheresis and bilateral oophorectomy, but did start to improve once second-line therapy was instituted. Similarly, Kramina *et al.*[137] described a patient whose catatonia, neurological signs and dysautomy were refractory to benzodiazepines, ECT and first-line immunotherapy but responsive to the combination of rituximab and cyclophosphamide, and Bowes *et al.*[141] described the case of a 15-year-old girl that not only had refractory symptoms to first-line immunotherapy with corticosteroids and intravenous immunoglobulins, but actually clinically deteriorated, with catatonic symptoms arising after, and only improving with second-line therapy, specifically rituximab. Keller *et al.*[142] reported the case of a 32-year-old woman that despite the urgent removal of a 5cm dermoid cyst followed by plasmapheresis, still presented fluctuations between communicable periods, catatonia, and extreme agitation, having only improved with rituximab as well.

Interestingly, Kuppuswamy *et al.*[138] published the case of a woman whose symptoms only resolved with the combination of IVIg (first-line therapy) and rituximab (second-line therapy).

Rituximab has also been effective in children as young as 20 months.[81,143] Because of the potential adverse effects of cyclophosphamide (malignancies, infertility, premature gonadal failure) most pediatricians only use it when the above treatments have failed.[90] In such cases, cyclophosphamide is often effective.[101,144]

In pregnancy women, immunomodulatory therapy can be effectively used.[77] McCarthy *et al.*[116] concluded that plasma exchange can be used safely in pregnancy but, should hypotension occur, it could decrease fetal perfusion.[116] Their experience with patients severely affected with anti-NMDAr encephalitis found that treatment with plasma exchange is superior to treatment with IVIg, as none of their patients were rendered antibody-negative when IVIg was used.

However, clinical improvement of symptoms doesn't seem to be clearly associated with a standard treatment, with the pattern of response to different therapies being quite diverse:

- Khadem *et al.*[104] described the case of a 57-year-old female with anti-NMDAr encephalitis treated with lorazepam + 12 sessions of ECT + methylprednisolone and without much clinical

improvement but with definite improvement in the next 8 months after bilateral removal of macroscopically and histologically normal ovaries +IVIg + cyclophosphamide.

- Schimmel *et al.*[58] described the case of a 12-year-old girl with anti-NMDAr encephalitis and catatonia who started to improve until almost full recovery after the initiation of plasmapheresis (started after the last steroid dose). The authors highlight that despite the improvement being apparently strongly time related to plasma exchange, a causative effect could not be inferred based on this single case, as a delayed steroid effect or simply a favorable natural course of the disease might have had justified the clinical response. This case is particularly interesting as previous literature mainly reported on remission after tumor resection and/or immunotherapy, which was not the case with this patient. The authors concluded that plasmapheresis might have at least accelerated recovery. Interestingly, Kamran Mirza *et al.*[145] described the case of a 14-year-old with anti-NMDAr encephalitis and catatonia who failed therapy with intravenous steroids, IVIg, one dose of rituximab, 7 sessions of ECT and who presented no improvement with plasmapheresis.
- Ryan *et al*.[70] described the case of a 37-year-old woman with anti-NMDAr encephalitis and catatonia treated with intravenous steroids and immunoglobulins, cyclophosphamide and rituximab with an almost full recovery after 4 months of treatment, with the authors attributing the favorable response primarily to rituximab.

DeSena *et al.*[146] published an interesting approach to treatment response variability in a pediatric population based on their clinical experience with their own patients followed by a literature review of other cases: they classified patients based on the type of predominant symptomatic manifestation and duration of disease, and found that there may be 3 clinical subtypes, with implications to treatment response and prognosis, and which could be used to the make a risk stratification regarding immunotherapy decisions:

- Type 1 or "classic" anti-NMDAr encephalitis: predominantly characterized by a catatonic or stuporous state, and with symptomatic duration of less than 60 days. The authors describe this group as the one with "fairly equal representations of periods of altered mental status, behavior problems, and movement disorders" whose prognosis is an intermediate one but will likely require aggressive immunotherapy.
- Type 2 or psychiatric-predominant anti-NMDAr encephalitis: no notable catatonic or stuporous state and predominant behavioral/psychiatric symptoms. This group was found to have excellent responses to plasmapheresis or other immunotherapies and appear to have the least residual deficits at follow-up.

- Type 3 or catatonia-predominant anti-NMDAr encephalitis: predominantly characterized by a catatonic or stuporous state, with symptomatic duration of 60 days or more. The authors found that this group were the poorest responders to treatment, even with aggressive immunotherapies.

Lee *et al.*[147] questioned whether metabolic changes observed with 18F-Fluorodeoxyglucose positron-emission tomography (FDG-PET) were correlated with the severity of the catatonic symptoms and clinical course. To investigate this, three patients with anti-NMDAr encephalitis showing variable degrees of catatonia were submitted to FDG-PET scans during the acute and recovery phase. The findings of hypermetabolism occurring in the fronto-temporo-parietal regions and bilateral basal ganglia in the patient with mild catatonia, but more widespread hypermetabolic regions, including the thalamus and brainstem, in the patients with more severe catatonia led to the conclusion that the extent of cerebral hypermetabolic changes correlates with the severity of catatonia accompanied by behavioral, motor, autonomic, and breathing abnormalities in anti-NMDAr encephalitis patients.

Early and aggressive immunotherapy has improved the natural history of the disease and anti-NMDAr encephalitis has a better prognosis than most forms of paraneoplastic encephalitis,[104,148] although it varies. As previously stated, 75% of cases recover with immunotherapy and tumor ablation (when present). Although recovery occurs without the need for tumor removal, symptoms tend to be more severe and more prolonged if it is not excised.[83] The remaining 25% of cases lead to severe sequelae and even death.[64] In a cohort[95] of 577 patients, including 211 children, the rate of mortality at 24 months was estimated at 7% due to uncontrolled disease progression, infections, or spread of tumor.

The outcome is usually good, with approximately 80% of patients having a substantial or full recovery, despite it being slow (weeks to months and even years)[90] with frequent protracted symptoms of frontal-limbic dysfunction (poor attention and planning, impulsivity, and behavioral disinhibition) and patients reporting amnesia for the entire event once the illness resolves.[81] However, long-term follow-up shows that these symptoms tend to improve, with autonomic instability, dyskinesias, level of consciousness and seizures improving first[101] and behavioral problems, decrease of verbal output, and social interactions being the last to recover. MRI signs of brain atrophy may also show improvement with long-term follow-up.[81,149]

Clinical outcome in children is similar to adults, with about half requiring second-line immune therapy.[94] In patients who do not improve with first-line immune therapy within the first week, second-

line immune therapy should be instituted as soon as possible as it has been shown to result in better outcomes if administered early.[94] Besides early treatment, low severity of disease within 4 weeks of onset and lack of need for ICU admission were also associated with a good outcome.[77] Türkdoğan *et al.*,[105] however, report a patient who had a dramatic recovery (in both clinical and laboratory settings) despite the presence of severe and long-lasting clinical symptoms and late onset of immunomodulatory therapy. For that reason, instead of adding one other immunomodulatory agent as a second-line treatment, the authors preferred long-term treatment of oral prednisolone with decreasing doses to prevent relapses.

Relapses are reported to occur in 7-25% of all cases,[37,64,95,150] with literature suggesting 20% in children.[101] It's not uncommon to find fully recovered patients who maintain detectable levels of antibodies in serum or CSF fluid, suggesting a potential for reactivation of the immune response.[151] The efficacy of chronic immunosuppression with azathioprine or mycophenolate mofetil in preventing relapses is unknown.[101] Identified risk factors for relapse include lack of immunotherapy at disease onset, delayed tumor removal and failure to identify a tumor.[77,96,150,152] There should be surveillance for occult neoplasm together with observation for recurrence or deterioration of psychiatric symptoms, which may signal relapse of encephalitis:

- In females of all ages previously diagnosed with anti-NMDAr encephalitis, recommendations include periodic surveillance for at least 2 years using MRI and ultrasound of the abdomen and pelvis.[80] Some papers report recommendations of continued yearly screening for tumor, particularly if the patient has a recurrence or remains symptomatic.[81]
- Formal information on tumor surveillance in males is not available. In one of the cases described by DeSena *et al.*,[146] a testicular tumor was noted 4 years after the diagnosis of anti-NMDAr encephalitis, and in a case described by Chapman *et al.*,[62] a testicular ultrasound and full-body PET were scheduled at 6-months intervals.
- Due to the cases reported – relapses at 6 and 15 years post-first presentation – Ramanathan *et al.*[153] propose that in patients without identified tumors, and particularly in those whose initial episode was not treated with immunomodulatory therapy, the period of ongoing tumor surveillance and antibody titer monitoring should be extended by as much as ten years.

Uchida *et al.*[154] report a case that illustrates the need to keep looking for tumors as the means to questioning why some patients are refractory to extensive treatment. In their case, they suggest that failure to improve after ovarian resection could be a marker of recurrent ovarian teratoma in this disorder: a woman with anti-NMDAr encephalitis with bilateral ovarian teratomas who was refractory

to tumor resection and early institution of immunotherapy, with persistently high titers of NMDAr antibodies over time, had a recurrent ovarian teratoma detected by pelvic CT, and after total enucleation of bilateral cystic teratomas, her titers decreased and she clinically improved.

Life after the acute event and subsequent rehabilitation is, however, not an easy process. After recovering consciousness, the psychiatric manifestations can reemerge – in fact, there is no evidence that effective treatment of the disorder prevents recurrence of catatonic or isolated psychiatric symptoms[132] –, and impulsivity, behavioral disinhibition, problems of attention, planning, social interaction, and memory deficits are usually difficult to manage, either at home or in rehabilitation centers. The latter usually have limited experience with the disorder, which tends to culminate in back-and-forth transfers with the hospital. A multidisciplinary approach involving nursing, psychiatrists, cognitive rehabilitators, and physiatrists, among others, is a necessary route to take in the future as it is highly rewarding for patients and families.[101,155–157] Curiously, van de Riet *et al.*[115] published a report describing how the admission of one teenager presenting with a severe first onset psychosis, with later deterioration to catatonia and autonomic instability, and with a subsequent diagnosis of anti-NMDAr encephalitis, was enough for the nursing team to recognize the symptomatic pattern of the disease and suspect its presence on a following admitted teenager with similar symptoms, which allowed for an earlier diagnosis.

Anti-NMDAr encephalitis in pregnancy may have a good outcome for both mother and baby,[116] but deaths of both mother and fetus have been described, like the case published by Keskin *et al.*,[158] where a 27-year-old pregnant woman who developed catatonia and autonomic instability died of septic shock after the demise of the fetus.

REFRACTORY CATATONIA SECONDARY TO ANTI-NMDA RECEPTOR ENCEPHALITIS

Psychiatric symptoms often show improvement that is gradual yet continuous, leading to full recovery without targeted intervention.[62] As discussed previously, it is rather frequent that psychiatric symptoms are indirectly managed through the etiologic management of the disease. An example that portrays this occurrence regarding catatonic symptoms is the case described by Ponte *et al.*,[159] who described the case of a 33-year-old man diagnosed with Paranoid Schizophrenia in 2009 and who presented to the psychiatric emergency department, 6 years after having abandoned follow-up, with persistent headaches, abnormal behavior and loss of motor skill, having been admitted to the

psychiatric ward under the diagnosis of Catatonic Schizophrenia. He later developed fluctuating catatonia, which did not respond to neuroleptics and benzodiazepines, and deteriorated to dysautonomic symptoms and seizures. He tested positive for anti-NMDAr antibodies but had no occult tumor. Etiologic treatment was initiated with high-dose steroids and IVIg, followed by cyclophosphamide, and the patient improved clinically. Similarly, a case described by Palakkuzhiyil *et al.*[160] reported on a middle-aged man whose catatonia did not respond to benzodiazepines, but improved with immunotherapy.

However, despite the expanding knowledge available, and as noted by Wilson *et al.*,[118] information on the management of psychiatric symptoms in these complex, often critically ill patients, is scarce, with medical literature mainly focusing on immunotherapy as the treatment for anti-NMDAr encephalitis. Given that anti-NMDAr encephalitis routinely first presents with psychiatric manifestations, including catatonia, that may persist and evolve throughout the illness course, it's necessary to address the importance of targeting persistent signs of catatonia related to the physiologic mechanisms of anti-NMDAr antibodies on the brain.[77,81,118] Of the little information available on specific management measures and responses regarding catatonia in a setting of anti-NMDAr encephalitis, it is often mentioned in passing as part of the case description or, if at all given some attention, is under a context of unexpected or negative response to a given treatment. Whereas the best treatment approach for anti-NMDAr encephalitis encompasses a combination of tumor resection, immunotherapy, intensive care, and rehabilitation, including physical therapy, discussions regarding the optimal approach to behavioral management are lacking.[62,108]

Some articles have reported on the use of ECT as a means to target catatonia in patients with autoimmune encephalitis,[4,12,110] but reports on the use of ECT in patients with catatonia specifically secondary to anti-NMDAr encephalitis are still equally scarce and urgently needed.[76,77,81,161,162]

So how are physicians addressing the catatonic syndrome in patients with anti-NMDAr encephalitis in the clinical practice? By following the general guidelines for the management of catatonia associated with psychiatric illness, which include the liberal use of benzodiazepines (lorazepam at regular intervals (e.g., 2 mg lorazepam every 6 hours)[163]/doses of up to 20-30mg of lorazepam per 24-hour period)[133] and ECT, as previously discussed.[59] These are measures with known effective treatment for catatonia in psychotic and mood disorders, but little is known about their therapeutic usefulness in catatonia associated with general medical and neurological illnesses.[62] Despite this, ECT is generally considered to be safe, even in medically compromised patients, and can be lifesaving in the setting of malignant catatonia,[118] regardless of etiology. Although adverse side effects from ECT are widely

feared, even despite the lack of published data on this topic, with subsequent barriers to its routine implementation in adolescents, medical literature reports it as being effective in treating 80% of cases of catatonia in young people.[164]

In the case of catatonia associated with anti-NMDAr encephalitis, some reports[12,161,165] have shown that 7 to 8 bilateral ECT treatments over 2–4 weeks have led to symptom remission.[163]

In the case of a 14-year-old with anti-NMDAr encephalitis described by Wilson *et al.*,[118] management of the primary immune-mediated encephalitis was accomplished using immunotherapy (rituximab) and malignant catatonia was addressed with ECT and high-dose lorazepam, until a dermoid cyst tumor was found and removed. ECT was then continued for 9 more treatments (before the tumor was removed, the patient had had 5 ECT treatments) and IVIg was added to rituximab. The patient gradually improved, received rehabilitation, and was well at 1-year follow-up. The authors hypothesized that ECT might have reversed the effect of antibodies on the brain, therefore providing protection until immunotherapy and tumor removal successfully stopped antibody production. Following this train of thought, the underlying argument would be that ECT could be beneficial in stabilizing the dysautonomy, hypermetabolism and agitated and psychotic states associated with anti-NMDAr encephalitis while a primary diagnosis and treatment are initiated.

Although molecular and genetic hypothesis to the etiopathogenesis and physiopathology of catatonia have emerged recently,[166] research has still been mainly focused on the neurochemical pathways through which it happens – with the main theories suggesting catatonia arises as the consequence of a dysregulation in the glutamate, GABA-A and dopamine pathways.[11] Yet, the ways through which ECT is beneficial in treating catatonia are still unknown. A study by Fumagalli *et al.*[167] in 2010 suggested that ECT may help regeneration of NMDA receptors damaged by autoantibodies by improving binding of the glutamate subunit on NMDA in the hippocampus. Watkins *et al.*[168] demonstrated in animal models of ECT action, that there is an elevation of messenger ribonucleic acid (mRNA) of the NMDA subunits NR2A and NR2B, mainly in the dentate gyrus of the hippocampus, leading to an upregulation of the NMDA receptor, although these changes only lasted for 48 hours.

Jones *et al.*[84] compiled some clinical cases which portray how improvement with ECT was independent from the response to the usual standard treatments (immunotherapy, tumor removal). The authors suggest that ECT may have a direct disease-modifying effect in anti-NMDAr encephalitis and, if that is indeed the case, that ECT might improve outcomes over standard therapy alone. As such, ECT as an adjuvant measure to surgical and immunological therapy in the acute care of this serious yet often reversible cause of catatonia warrants further study:

- Matsumoto *et al.*[169] described an 18-year-old man with anti-NMDAr encephalitis who fully recovered from catatonia after 13 ECT treatments together with antipsychotics but no immunotherapy.
- Mann *et al.*[170] reported the case of a 14-year-old girl with rapid onset of psychosis and delirium progressing to mutism, who was diagnosed with anti-NMDAr encephalitis after 6 weeks of work-up. She failed to improve with 3 days of IVIg, then a week of risperidone treatment, and finally a partial trial of rituximab. She started ECT because of progressively worsening catatonia, with rapid but only partial improvement, leaving residual mood lability and sleep disturbance. She then received a series of immunotherapies as well as risperidone and lorazepam, making a gradual recovery with some residual cognitive problems 8 months after the onset of symptoms.

Ramanathan *et al.*[153] reported two cases where patients demonstrated complete recovery without immunomodulatory therapy or tumor identification, with Patient 2 being only the second report of complete recovery with ECT as the sole therapeutic intervention, the first being described recently by Matsumoto *et al.*[169]

Braakman *et al.*[161] presented the case of a previously healthy 47-year-old male who presented with progressive psychiatric symptoms following an upper respiratory tract infection, whose extensive investigations performed did not reveal any abnormality, and whose CSF showed pleocytosis. These limited findings motivated initial therapy for a viral encephalitis and subsequently for encephalitis lethargica with intravenous lorazepam and 3 days of intravenous methylprednisolone. However, his psychiatric symptoms failed to resolve and so he underwent 7 sessions of bilateral ECT, which eventually induced remission. All symptoms, including mutism, hallucinations, oculogyric crises and extrapyramidal symptoms resolved and he returned to work within 2 years. The definite diagnosis of anti-NMDAr encephalitis was only made later with retrospective analysis of his CSF, which revealed anti-NMDAr antibodies.

Gough *et al.*[122] described the case of a previously healthy 71-year-old female who presented to her general practitioner (GP) with malaise and bilateral shoulder pain. Because her erythrocyte sedimentation rate (ESR) was raised at 45 mm/h and C-reactive protein (CRP) levels were raised as well, she was prescribed prednisolone, with Polymyalgia Rheumatica as the suspected diagnosis. By the start of the medication she started to show signs of low mood, and obsessional and paranoid thoughts. Once completed her course of steroids, she presented again to her GP, which decided to commence her on fluoxetine, buspirone and diazepam as symptomatic relief. Despite this, her

psychiatric symptoms continued to deteriorate, and she developed catatonia, posturing with psychotic symptoms, paranoid thoughts, nihilistic delusions and auditory hallucinations, associated with significant loss of weight and inability to fulfil her activities of daily living. By this time, she was admitted to a psychiatric ward (2 months after her initial presentation to the GP): she appeared withdrawn, confused, disorientated and was responding to auditory hallucinations. Her general physical examination and normal, as was her neurological one. She maintained a raised ESR and was found to have a raised leukocyte count (with neutrophilia), raised urea and creatinine, alanine transaminase (ALT) and bilirubin. Lumbar puncture for CSF analysis was not performed, as the doctors did not feel there was indication for such at the time, and a CT scan of her head did not show any abnormality. The patient was started on risperidone and sertraline but stopped shortly afterwards because she became dizzy and had an unresponsive episode, which motivated an admission to the emergency department for further investigation, with no physical cause being identified. Mirtazapine, venlafaxine and olanzapine also failed to improve her symptoms. By then she remained severely depressed with persistent catatonia and psychotic features, and so an ECT regime was started. However, after the fourth cycle of ECT, the patient fell and fractured the neck of her femur, which required surgery and a 2-week admission to an orthopedic ward, thus stopping her ECT regimen. Once she returned to the psychiatric unit her serum autoantibodies screen test results (sent on admission) became available and showed low positivity for anti-NMDAr encephalitis. No evidence of malignancy was detected on CT scan of chest, abdomen and pelvis. The Neurology unit was contacted, and plasmapheresis was started associated with methylprednisolone, followed by prednisolone, soon tapered down. However, her antibodies titers remained on the low-positive range and despite the plasmapheresis, corticosteroids and multiple psychotropics later administered (quetiapine, lithium and further venlafaxine), the patient's symptoms remained severe. A second course of ECT was then initiated, with 8 cycles being completed. This time, however, the patient presented a marked recovery, with her mood improving significantly and with no psychotic symptoms. Her antibody titers were repeated and undetectable and the patient was discharged home at her premorbid level.

Sunwoo *et al.*[171] defend that ECT may be an option for life-threatening catatonia and medically refractory dyskinesia in patients with anti-NMDAr encephalitis; their 27-year-old female patient developed catatonia even after the disease had been detected early and an ovarian tumor removed followed by IVIg and administration of rituximab. Catatonia was refractory to benzodiazepines and dyskinesia and so severe she had to had continuous infusions of a neuromuscular blocker, with escalating doses, suggesting that she wasn't improving, even with co-administration of rituximab. Finally, ECT was started and she responded to it.

Amorim *et al.*[172] describe an interesting case of a 73-year-old woman that was referred to the neurology clinic for evaluation of cognitive decline and catatonia. Despite treatment with benzodiazepines, antipsychotics and 12 ECT sessions (with no electrocardiographic seizures documentation despite escalating electrical doses), her catatonic symptoms persisted. She was later found to have a mature ovarian tumor, which was removed, but catatonia failed to improve, even with benzodiazepines. ECT was repeated, this time with achievement of electrographic seizures, and there was partial improvement. Anti-NMDAr antibodies were negative in the CSF, but the authors stress that these were obtained nearly 10 months after the surgery. In the meanwhile, due to ongoing sleep disturbance, she was prescribed zolpidem (a GABA-A receptor agonist, routinely used as a hypnotic in the short-term treatment of insomnia) 5 mg at bedtime and shortly after its administration, the patient improved dramatically. However, the effect lasted only 6-10 hours until she would return to her baseline catatonic-state, with progressively shorter periods of response. A few case reports[173,174] of catatonia responsive to zolpidem have been described in the literature, and it has been proposed that it could be used as a pharmacological test for the clinical diagnosis of catatonia.

Medina and Cooper[175] report on the case of a highly educated woman in her late 20s whose refractory catatonia secondary to anti-NMDAr encephalitis was successfully treated with ECT. What's interesting in this case is that, contrary to other reports where the authors only described the improvement of the catatonic syndrome, this patient performed the Clock Drawing Test (CDT) pre-ECT, after the second ECT session, after the sixth and final ECT session and at 6-months follow-up, with the difference between the first and second drawing being remarkable, with a clear improvement following the first two sessions of ECT.

Recently, in February 2019, Moussa *et al.*[176] described the case of a previously healthy 16-year-old with anti-NMDAr encephalitis and catatonia, whose catatonic symptoms remained refractory to trials of lorazepam and zolpidem. Similarly, catatonia did not resolve with etiologic treatment: despite intensification of both first-line treatment with IVIg and second-line treatment with rituximab and a second course of methylprednisolone. In fact, she persisted with episodes of agitation, rigidity, sleep disturbance, mutism, facial twitching, drooling, and autonomic instability, leading to the diagnosis of malignant catatonia. Her BFCRS was 27. Because of this, she was started on ECT. Over the course of her 8 treatments given thrice weekly, her BFCRS dropped from 27 to 2 and her mental status evaluation (through the CDT) showed marked improvement in visuospatial, motoric, and cognitive functioning prior to ECT, during the ECT course and post-ECT, with the patient's mother noting that the patient displayed more of her typical personality and mannerisms. However, the patient remained mute post-ECT and was discharged home on melatonin, levetiracetam, tapering doses of prednisone and

lorazepam, and additional IVIg treatments, as well as intensive outpatient rehabilitation including speech, physical and occupational therapy. At her 6-week post-ECT clinic appointment, her verbal abilities and communication skills appeared normal.

Also in 2019, Tanguturi *et al.*[177] looked to thoroughly review the use of ECT in the treatment of catatonia secondary to anti-NMDAr encephalitis, concluding that its use is indicated in the treatment of catatonia, particularly in cases of resistant catatonia, failure of first-line immunotherapy and when plasma exchange is not available. They also report that the use of synergistic ECT with benzodiazepines could help with faster recovery and shorter time spent in the hospital, and recommend the creation of a treatment algorithm for anti-NMDAr encephalitis that includes both benzodiazepines and/or ECT to manage catatonic symptoms in addition to immunotherapy to target the antibody development, with further research needed to identify the treatment specifications such as length of time of treatment and parameters for response to treatment.

Similarly, Warren *et al.*[178] looked to systematically ascertain whether ECT in the treatment of anti-NMDAr encephalitis was safe and could improve psychiatric outcomes. In their systematic review, published in 2019 and with analysis of cases published between 2007 and June 2018, 30 cases were selected. Cases selected had to had anti-NMDAr encephalitis formally diagnosed by positive serum or CSF IgG antibodies with catatonia clearly documented under established criteria. Treatment response and outcome was based on the information provided in the case reports and categorized as *resolved*, *improved*, *no improvement* or *deterioration.* Of the 30 cases, 26 cases (86.7%) developed catatonia during the illness course and 3 additional cases, despite not having a documented catatonia, had a BFCSI greater than 2, which indicates catatonic symptoms. The most common catatonic symptoms were, in descending order: excitement, immobility/stupor, mutism, withdrawal, posturing, rigidity, stereotypy and perseveration. Of the 24 cases documented to have started ECT due to catatonia, 5 (20.8%) had resolved catatonia, 8 (33.3%) had improved catatonia and 4 (16.7%) didn't show any signs of improvement. The last 4 (16.7%) remaining cases had no statements on ECT outcomes. Both excited and stuporous catatonic symptoms were effectively treated in these cases at a comparable efficacy. Data pertaining to the effectiveness of ECT on overall psychiatric symptoms was also reported: of the 23 cases on information regarding ECT effectiveness, 4 had complete resolution of psychiatric symptoms without any immunotherapy and after treatment resistance had been noted with psychotropics, and 15 (65.2%) noted improvement of psychiatric symptoms, with 9 of those having improvement prior to immunotherapy; in the 6 cases which improved with a combination of ECT and immunotherapy, ECT was started due to insufficient response to immunotherapy. The authors conclude what other authors have suggested throughout time based on their personal clinical

experience: in anti-NMDAr encephalitis ECT appears to be a safe, effective adjuvant treatment, especially for psychiatric symptoms such as catatonia, with no lasting adverse consequences for the patient in the less than 15% of cases where it was prematurely stopped.

CONCLUSION

Catatonia is a psychiatric symptom that has been established to happen secondarily to either primary psychiatric disease or organic disease, specifically anti-NMDA receptor encephalitis. Therefore, two major conclusions can be drawn that serve as recommendations for both physicians and scientists:

1. When investigating catatonic symptoms, one must consider anti-NMDA receptor encephalitis as a possible cause;
2. When dealing with a patient diagnosed with or suspected of having anti-NMDA receptor encephalitis, one must be aware that catatonia may be a potential developing symptom.

In clinical practice, psychiatric symptoms, including catatonia, are often indirectly managed through the etiologic treatment of the underlying encephalitis, with first-line therapy consisting of methylprednisolone, intravenous immunoglobulins and/or plasmapheresis, and second-line therapy composed of rituximab and/or cyclophosphamide.

Response to treatment is, however, variable and catatonic symptoms may not resolve. This paper has also summarized some examples of catatonia secondary to anti-NMDA receptor encephalitis refractory to first-line symptomatic treatment with benzodiazepines and/or etiologic that were effectively and safely managed with the use of electroconvulsive therapy. Therefore, as our final recommendation:

3. In catatonia secondary to anti-NMDA receptor encephalitis that does not respond to first-line therapy with benzodiazepines and/or etiologic treatment, we recommend consideration of the use of electroconvulsive therapy as a therapeutic option.

The main aim of this paper is, however, to alert the medical and scientific community of the close relation between these two entities – anti-NMDA receptor encephalitis and catatonia – and that they may not be as rare as once thought and, as so, cannot go unnoticed by any psychiatrist or neurologist. Further attention and investigation on this relation should be encouraged.

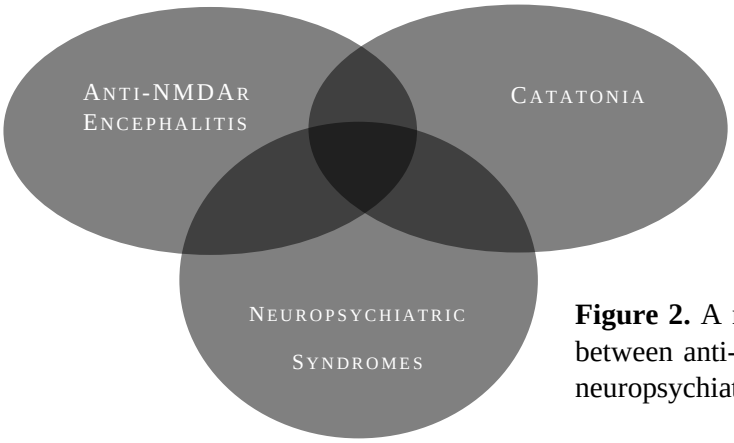


Figure 2. A new area of potential research: the correlation between anti-NMDAr encephalitis and catatonia in various neuropsychiatric disorders.

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And finally, but certainly not the least, to *my people* – my Lisbon light, my prophylaxis of the blues, and the home I carry inside.

TABLES

Table 1. Summary of the clinical cases of patients with catatonia secondary to anti-NMDA receptor encephalitis mentioned in this literature review. ♀*: female;* ♂*: male;* •*: patients who were diagnosed with anti-NMDAr encephalitis only after being managed and discharged; US: ultrasound; CT: computed tomography; IVIg: intravenous immunoglobulins; ECT: electroconvulsive therapy; CDT: Clock Drawing Test.*

AUTHORS (YEAR)	PATIENT'S AGE (YEARS) AND GENDER	CATATONIA	MANAGEMENT & OUTCOME
Khadem *et al.* (2009)	57 ♀	Developed over the course of the disease, with autonomic deterioration	Bilateral oophorectomy (in a postmenopausal woman with negative US for ovarian lesion but small hypoechoic lesion in the right ovary on CT scan) + IVIg + Cyclophosphamide (with improvement in the following 8 months, but remained with difficulty in managing tasks of daily living)
Parratt *et al.* (2009)	21 ♀	Developed over the course of the disease	*The authors refer they chose to defer high-dose corticosteroids to avoid the possible psychiatric side effects that could confuse the clinical response.* **1st** IVIg (with further deterioration) **2nd** Methylprednisolone (behavior remained markedly abnormal) **3rd** Plasmapheresis (without clinical improvement) **4th** Bilateral oophorectomy (no ovarian tumor was identified microscopically) **5th** Rituximab (with clinical improvement; 14 months later, her neuropsychological test showed her cognitive performance to be in the high–average range across domains)
Schimmel *et al.* (2009)	12 ♀	Developed over the course of the disease, with later autonomic deterioration	Plasmapheresis (with improvement over 4 weeks until almost full recovery; after 4 weeks of rehabilitation only showed minimal dysfunction of short-term memory)
Braakman *et al.* (2010)	47 ♂ •	Developed over the course of the disease	Lorazepam + Methylprednisolone + ECT (7 cycles) (with disappearance of catatonic symptoms; at 1-year follow-up, the patient was back at his former job)
Consoli *et al.* (2011)	17 ♀	Developed over the course of the disease, with progression to malignant catatonia and autonomic instability	**1st** Olanzapine + Loxapine + Clonazepam (with further deterioration) **2nd** Lorazepam (remained catatonic) **3rd** Prednisone + Cyclophosphamide + Plasmapheresis (progressively improved, but the patient revealed many neurological sequelae) **4th** IVIg (with clinical improvement; post-cognitive sequelae disappeared within 2 years)

Kamran Mirza *et al.* (2011)	14 ♀	Developed over the course of the disease, with progression to malignant catatonia	**1st** Lorazepam (with mild improvement in catatonic symptoms) **2nd** IVIg + Rituximab (resulting in hypotension, flushing, diaphoresis, fever, and coarse breath sound, and later descending into malignant catatonia) **3rd** ECT (7 cycles) **4th** Plasmapheresis (without clinical improvement) **5th** Cyclophosphamide (with decreased impulsivity but minimal change in aggression; she was discharged to a rehabilitation center with a recommendation for surveillance imaging)
Mann *et al.* (2012)	14 ♀	Developed over the course of the disease, with autonomic deterioration	**1st** Lorazepam (with temporary but dramatic improvement) **2nd** Rituximab (not completed because of autonomic instability and worsening catatonia) **3rd** ECT (with autonomic stabilization and partial clinical improvement; no mention of specific catatonic symptoms; remained aggressive and impulsive) **4th** Plasmapheresis + Rituximab + Cyclophosphamide followed by Risperidone + Lorazepam (with relevant clinical improvement)
Matsumoto *et al.* (2012)	18 ♂ •	Presenting symptom	**1st** Antipsychotics + Lorazepam + Sodium Valproate (with reduction only in confusional state) **2nd** ECT (13 cycles) + Antipsychotics (with full recovery and without need for medication at his 1-year follow-up appointment)
McCarthy *et al.* (2012)	32 ♀ (pregnant)	Presenting symptom, with autonomic deterioration	**1st** Methylprednisolone (with further deterioration) **2nd** Plasmapheresis (with complete recovery) *A cystic teratoma was later found and removed when she gave birth via caesarean section.*
Ramanathan *et al.* (2013)	31 ♀	Presenting symptom, excited type	**1st** Methylprednisone + IVIg + Plasmapheresis (without sustained improvement) **2nd** Rituximab (with good effect)
	17 ♀ •	Presenting symptom	**1st** Benzodiazepines (with absence of response) **2nd** ECT (with significant improvement within 2 weeks and complete recover over the span of 1 year)
Ryan *et al.* (2013)	37 ♀	Presenting symptom, with autonomic deterioration	Steroids + IVIg + Cyclophosphamide + Rituximab (with almost complete recovery after 4 months of treatment)
van de Riet *et al.* (2013)	15 ♀	Progressed over the course of the disease, with autonomic deterioration	Methylprednisolone + IVIg + Rituximab + Rehabilitation (with almost complete return to their premorbid level of functioning)

	17 ♀	Progressed over the course of the disease, with autonomic deterioration	Prednisone + IVIg + Plasmapheresis + Cyclophosphamide + Rehabilitation (with almost complete return to her premorbid level of functioning)
Verfaillie *et al.* (2013)	18 ♀	Progressed over the course of the disease, with autonomic deterioration	**1st** Methylprednisolone + Plasmapheresis (with insufficient response) **2nd** Methylprednisolone + Plasmapheresis + Cyclophosphamide (with a slow but consistent recovery; 2 months later, she was discharged with only discrete frontal signs)
Wilson *et al.* (2013)	14 ♀	Presenting symptom, with progression to malignant catatonia	Lorazepam + ECT (14 cycles) + Left salpingo-oophorectomy (ovarian dermoid lesion) + high-dose steroids + Rituximab + IVIg (with catatonia almost completely resolved; at 1-year follow-up the patient was at her cognitive and physical baseline)
Gulyayeva *et al.* (2014)	22 ♀	Developed over the course of the disease	**1st** IVIg + Methylprednisolone (with persistence of behavioral abnormalities) **2nd** Rituximab + Plasmapheresis + High-dose Steroids + IVIg (with clinical improvement, but after 4 months she still demonstrated difficulties in cognition and executive function)
	19 ♀	Developed over the course of the disease, with later autonomic deterioration	Laparoscopic oophorectomy (ovarian teratoma) + IVIg + Plasmapheresis + Steroids + Risperidone (with clinical improvement, without cognitive sequelae after 10 months)
Keller *et al.* (2014)	32 ♀	Developed over the course of the disease (associated with psychotic symptoms)	**1st** Diazepam + Phenytoin + Sodium Valproate (the patient had seizures) (without improvement) **2nd** Cystectomy (dermoid cyst) + Plasmapheresis (mental status improved slightly but was still fluctuating between communicable periods, catatonia and extreme agitation) **3rd** Rituximab + Cognitive Rehabilitation (with gradual improvement, with almost full return to baseline 3 months later)
Kruse *et al.* (2014)	16 ♀	Developed over the course of the disease (associated with psychotic symptoms)	**1st** Methylprednisolone + Plasmapheresis + Olanzapine (with persistence of echolalia, waxing and waning mental status, intermittent agitation, catatonia, and auditory and visual hallucinations) **2nd** Lorazepam + Diphenhydramine (for milder agitation) + Plasmapheresis (with marked improvement of mental status)
Kuppuswamy *et al.* (2014)	35 ♂	Developed over the course of the disease	**1st** Olanzapine (with symptoms worsening) **2nd** Lorazepam + Methylprednisolone > Prednisone + Plasmapheresis + Azathioprine + Quetiapine (with resolution of symptoms and a return to his prior functioning at 4 months follow-up)

	30 ♀	Developed over the course of the disease	**1st** Methylprednisolone + Lorazepam (with minimal clinical improvement) **2nd** Prednisone + Plasmapheresis (with minimal improvement) **3rd** IVIg + Rituximab (with return to baseline)
Türkdoğan *et al*. (2014)	15 ♀	Developed over the course of the disease	**1st** IVIg (with slight and temporary clinical improvement) **2nd** Methylprednisolone > Prednisone (with significant clinical improvement)
Bowes *et al.* (2015)	15 ♀	Developed over the course of the disease	*Before the manifestation of catatonic symptoms, the patient had already had Methylprednisolone > Prednisone + IVIg (with further deterioration)* **1st** Rituximab (with clinical improvement)
Jones *et al.* (2015)	17 ♂	Developed over the course of the disease (associated with psychotic symptoms)	**1st** Lorazepam (without improvement) **2nd** Olanzapine + Quetiapine (without improvement) **3rd** ECT (2 cycles) (with improvement of catatonic symptoms) (CSF results leading to the diagnosis of anti-NMDAr encephalitis only came back after the 2nd cycle of ECT) **4th** IVIg (gradual improvement; no additional follow-up available)
Kiani *et al.* (2015)	32 ♀	Developed over the course of the disease	**1st** Psychotropic medication (not specified) (without improvement) **2nd** Methylprednisolone (2 courses, with clinical improvement; 6 months later she was at her premorbid level)
Kramina *et al.* (2015)	15 ♀	Developed over the course of the disease (associated with psychotic symptoms), with later autonomic deterioration	**1st** Haloperidol + Midazolam (with no beneficial effect) **2nd** ECT (with no improvement) **3rd** Methylprednisolone + IVIg + Plasmapheresis (with no response; had two successful cardiopulmonary reanimations) **4th** Rituximab + Cyclophosphamide (with clinical improvement; 1 year later she had returned to her normal routine but still had mood swings, difficulty in making decisions and mixed left and right)
Heekin *et al.* (2015)	24 ♀	Developed over the course of the disease, with later autonomic deterioration	**1st** ECT (3 cycles) (before her 4th cycle she experienced several generalized tonic-clonic seizures and had to be intubated) **2nd** Methylprednisolone + IVIg (with resolution of catatonia) **3rd** Methylprednisolone > Prednisone (for impaired cognition, with clinical improvement and at her premorbid level at her 8-month follow-up appointment)

Yoshimura *et al.* (2015)	47 ♀ •	Presenting symptom	*She had been diagnosed with depression with catatonic stupor at 44 and 46 years of age, and bipolar disease.* Quetiapine + Lithium + Lorazepam (with catatonic and depressive symptoms gradually resolving; anti-NMDAr antibody test was negative 14 months after discharge)
	48 ♀ •	Presenting symptom	**1st Admission:** Quetiapine + Lithium + Lorazepam (gradually improved and was discharged 2 months after) **2nd Admission (5 months after, with the same symptoms):** Quetiapine + Nitrazepam (with symptoms resolving after 1 week)
Gough *et al*. (2016)	71 ♀	Developed early in the course of the disease (associated with depressive and psychotic symptoms)	**1st** Plasmapheresis + Methylprednisolone > Prednisolone (mood and speed of thinking improved, but depression remained, and paranoia worsened; no mention of specific catatonic symptoms) **2nd** Prednisolone + Quetiapine + Lithium + Venlafaxine (no mention of specific catatonic symptoms, but the authors report that her symptoms remained severe) **3rd** ECT (8 cycles) (with marked and rapid recovery with function regain at her premorbid level)
Mythri *et al.* (2016)	26 ♀	Developed over the course of the disease	Immunotherapy (not specified) (with clinical improvement of catatonic symptoms)
Ponte *et al.* (2016)	33 ♂	Presenting symptom, with later autonomic deterioration	**1st** Neuroleptics and Benzodiazepines (unsuccessful) **2nd** High-dose Steroids + IVIg + Cyclophosphamide (with relevant clinical improvement)
Sunwoo *et al.* (2016)	27 ♀	Developed over the course of the disease, with later autonomic instability	*Before catatonia appeared, she had already had an ovarian mass removed + IVIg + Rituximab.* **1st** Multiple Antiepileptics (with no response) **2nd** Lorazepam > Diazepam > Clonazepam (with no effect) **3rd** Olanzapine (with signs suggestive of Malignant Neuroleptic Syndrome) **4th** Cisatracurium (neuromuscular blocker) + Rituximab (both for uncontrolled dyskinesia) (drugs persistently required, indicating that her clinical status did not change for several months) **5th** ECT (13 cycles) (with improvement of dyskinesia and catatonia, but with persistence of cognitive disabilities)
Chatterjee *et al.* (2017)	27 ♀	Developed over the course of the disease	**1st** Lorazepam **2nd** Methylprednisolone + Plasmapheresis (with the patient becoming stable and oriented; she completely recovered in 1 month)

Fisher *et al.* (2017)	27 ♀	Presenting symptom, with later autonomic deterioration	**1st** IVIg + Corticosteroids (with mental status fluctuation) **2nd** Rituximab (with mental status improvement; 13 months later she had chronic daily headaches, fatigue, and showed mild impairment to recent and remote memory)
Hermans *et al.* (2017)	25 ♀	Developed over the course of the disease, with autonomic deterioration	**1st** Lorazepam (with increasing confusion and agitation, fever, tachycardia and autonomic instability) **2nd** Methylprednisolone (short course, without significant effect) **3rd** ECT (1 cycle and then stopped because antibody results came back positive on the same day) **4th** Plasmapheresis + Methylprednisolone (some improvements but catatonia remained) **5th** Plasmapheresis + Methylprednisolone + Mycophenolic Acid (catatonia disappeared; 10 months after initial presentation she was at her premorbid level)
Medina and Cooper (2017)	Late 20s ♀	Developed over the course of the disease	**1st** IVIg + Corticosteroids (with minimal improvement) **2nd** Lorazepam (with partial response) **3rd** ECT (6 cycles) (with largely resolved catatonic symptoms and improvement in the CDT)
Tsutsui *et al.* (2017)	24 ♂ •	Developed over the course of the disease	*3 years before the patient had an episode of catatonia, symptomatically treated (not specified) + phenytoin (for a seizure), with a good outcome; he was discharged a month later but abandoned follow-up.* **1st** IVIg + Phenytoin (the patient had seizures) **2nd** Steroid pulse therapy (with some effects) **3rd** Risperidone + Levomepromazine (with gradual clinical improvement, discharged 2 months later without deficit)
Voice *et al.* (2017)	17 ♀	Presenting symptom, with later autonomic deterioration	**1st** Left ovarian cystectomy (mature teratoma) (with maintenance of disorientation, catatonia and autonomic instability) **2nd** Methylprednisolone + IVIg + Plasmapheresis (with clinical improvement and no signs of relapse at her follow-up 14 months later)
Palakkuzhiyil *et al.* (2018)	47 ♂	Developed over the course of the disease	**1st** Lorazepam (with persistence of catatonic symptoms) **2nd** Immunotherapy (not specified) (with improvement of catatonia)
Keskin *et al.* (2019)	27 ♀ • (pregnant)	Developed over the course of the disease, with autonomic deterioration	**1st** Methylprednisolone (regimen repeated twice, with no clinical improvement in both attempts) **2nd** Plasmapheresis (initiated and applied twice but had to be stopped due to infection and hypotension) *Vaginal bleeding and hypotension occurred, with fetal demise, and the patient died of septic shock.*

Moussa *et al.* (2019)	16 ♀	Developed over the course of the disease, with progression to malignant catatonia	**1st** Lorazepam + Zolpidem (unsuccessful) **2nd** IVIg + Rituximab + Methylprednisolone (unsuccessful) **3rd** ECT (8 cycles) (improved, but remained mute) **4th** Discharged on Melatonin + Levetiracetam + Prednisone + Lorazepam + IVIg + Rehabilitation (with normal appearing verbal abilities and communication skills at her 6-week post-ECT follow-up appointment)

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