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Catatonia associated with epileptic seizures: a systematic review

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Abstract

Catatonia is a neuropsychiatric syndrome with multiple secondary causes. Its association with epileptic seizures is a rare phenomenon that is poorly understood, so the objective of this review is to summarize the clinical characteristics and management of these patients, looking at epilepsy as a possible cause for catatonia. This systematic review included all case reports of patients with catatonia meeting ICD-11 criteria associated with epileptic seizures, published until December 2021 in PubMed. Case reports were synthesized and results were expressed as percentages. In total, 42 articles with 52 case reports were included. Most of the patients were adults with a dispersed age (mean age 44.9 ± 19.3), slightly more males (59.6%), with a psychiatric history (76.9%) mainly of affective disorders (26.9%) or psychotic episodes (13.5%) and/or a neurological history (61.5%) of epileptic seizures (38.5%) or head trauma (13.5%). Their clinical presentation consisted mostly of decreased psychomotor activity (mutism: 94.2%; stupor: 78.8%; staring: 57.7%; negativism: 36.5%) with some abnormal psychomotor activity (catalepsy: 40.4%; rigidity: 40.4%; waxy flexibility: 23.1%; posturing: 21.2%) and it was common the occurrence of clinical epileptic seizures (51.9%), mostly generalized tonic-clonic (23.1%). Almost all electroencephalograms (97.9%) and almost half of brain imaging exams (47.4%) performed had abnormal findings. The epileptic activity was mainly generalized (50%) and associated with primary epilepsy (30.8%), iatrogenesis (23.1%), other secondary aetiologies (25%) or unknown causes (21.2%). Most improved with antiepileptic therapy (87.5%) and had a complete remission (86.5%). Catatonia secondary to epileptic seizures often has a nonspecific clinical presentation and appears in patients with previous psychiatric diagnoses, so any patient with catatonia should be properly investigated to avoid misdiagnosis and ineffective treatments.

Keywords: Catatonia, Kahlbaum syndrome, Epilepsy, Seizure, Ictal.

Resumo

A catatonia é uma síndrome neuropsiquiátrica com múltiplas causas secundárias. A sua associação com crises epilépticas é um fenómeno raro e pouco compreendido, pelo que o objetivo desta revisão é resumir as características clínicas e a abordagem destes doentes, olhando para a epilepsia como uma possível causa de catatonia. Esta revisão sistemática incluiu todos os casos clínicos de doentes com catatonia com critérios da ICD-11 associada com crises epiléticas, publicados até dezembro de 2021 na PubMed. Os casos clínicos foram sintetizados e os resultados foram expressos em percentagens. No total, foram incluídos 42 artigos com 52 casos clínicos. A maioria dos doentes eram adultos com idade dispersa (idade média 44,9 ± 19,3), um pouco mais do sexo masculino (59,6%), com história psiquiátrica (76,9%) principalmente de perturbações afetivas (26,9%) ou episódios psicóticos (13,5%) e/ou história neurológica (61,5%) de crises epiléticas (38,5%) ou traumatismo craniano (13,5%). A sua apresentação clínica consistiu principalmente em atividade psicomotora diminuída (mutismo: 94,2%; estupor: 78,8%; olhar fixo: 57,7%; negativismo: 36,5%), com alguma atividade psicomotora anormal (catalepsia: 40,4%; rigidez: 40,4%; flexibilidade cérea: 23,1%; postura: 21,2%) e foi comum a ocorrência de crises epiléticas clínicas (51,9%), principalmente tónico-clónicas generalizadas (23,1%). Quase todos os eletroencefalogramas (97,9%) e quase metade dos exames de imagem cerebral (47,4%) realizados apresentaram achados anormais. A atividade epilética foi principalmente generalizada (50%) e associada a epilepsia primária (30,8%), iatrogenia (23,1%), outras etiologias secundárias (25%) ou causas desconhecidas (21,2%). A maioria melhorou com terapêutica antiepilética (87,5%) e teve remissão completa (86,5%). A catatonia secundária a crises epiléticas tem uma apresentação clínica muitas vezes inespecífica e surge frequentemente em doentes com diagnósticos psiquiátricos prévios, pelo que qualquer doente com catatonia deve ser investigado adequadamente de modo a evitar diagnósticos errados e tratamentos pouco eficazes.

Palavras-chave: *Catatonia, Síndrome de Kahlbaum, Epilepsia, Convulsão, Ictal.*

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Introduction

Catatonia is a psychomotor syndrome first described by Kahlbaum in 1874, in his publication *Die Katatonie oder das Spannungsirresein* (Kahlbaum, 1874). Therefore, catatonia is also known and called by some authors Kahlbaum syndrome (Barnes et al., 1986; Fink & Taylor, 2009; Peralta et al., 1997; Rao et al., 2012). In his publication, Kahlbaum described 26 cases of patients with catatonia, highlighting the association with mood disorders and organic brain diseases, including epilepsy, alcoholism, malaria, syphilis and tuberculosis. In 1893, the concept of catatonia was incorporated by Kraepelin into a clinical picture of degenerative psychosis, which he called dementia praecox, defining it as having a psychological origin. Later, Bleuler defined the term schizophrenia, including catatonia as a subtype of schizophrenia, and reinforced its psychogenic origin. Catatonia was, at this point, considered a persistent and generalized state of blocking that worked as a protection mechanism from situations of suffering. Due to the influence of the work of Kraepelin and Bleuler, catatonia has been regarded as a purely psychiatric condition typically associated with schizophrenia (Barnes et al., 1986; Johnson, 1993; Kahlbaum, 1874). The Diagnostic and Statistical Manual of Mental Disorders contemplated the possibility of an organic cause of catatonia for the first time in its fourth edition (DSM-IV) published in 1994, in which the diagnosis of catatonic disorder due to a general medical condition was considered (American Psychiatric Association, 1994). Since 1996, the Bush-Francis Catatonia Rating Scale (BFCRS), is the most important validated tool for the screening and assessment of the severity of catatonia, diagnosing it by the presence of at least 2 of the first 14 items: immobility or stupor, mutism, staring, posturing or catalepsy, grimacing, echopraxia or echolalia, stereotypy, mannerisms, verbigeration, rigidity, negativism, waxy flexibility, withdrawal and excitement (Bush et al., 1996). The fifth and last version of the DSM published in 2013 (DSM-5) considers catatonia as an entity independent of schizophrenia and includes the diagnoses of catatonia associated with another mental disorder, catatonic disorder due to another medical condition and unspecified catatonia. Furthermore, it highlights the importance of neurological and metabolic conditions as a secondary cause of catatonia (American Psychiatric Association, 2013). In the International Statistical Classification of Diseases and Related Health Problems, the diagnosis of secondary catatonia appeared firstly in the tenth

version (ICD-10), which was supported by the World Health Organization (WHO) assembly in 1990 and began to be used in 1994 by member states. Furthermore, in this version, catatonia was only considered as a subtype of schizophrenia, not admitting the possibility of being a manifestation of other psychiatric disorders (World Health Organization, 1990). In the eleventh and latest version of the ICD, which was approved in 2019, but which will only come into effect in 2022 (ICD-11), in addition to recognizing the possibility of catatonia having a secondary cause, the diagnoses of catatonia associated with other mental disorder, induced by substances or medications and unspecified were also introduced (World Health Organization, 2019). Table 1 summarizes the evolution of the diagnostic classification of catatonia. Catatonia is nowadays defined in the fifth edition of the DSM by the presence of three or more of 12 psychomotor symptoms or signs, including stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerism, stereotypy, agitation, grimacing, echolalia and echopraxia (American Psychiatric Association, 2013). The ICD-11 defines catatonia as a syndrome characterized by the co-occurrence of several symptoms or signs of decreased, increased, or abnormal psychomotor activity, requiring at least three of fifteen clinical manifestations, including staring, ambitendency, negativism, stupor, mutism, extreme hyperactivity/agitation or impulsivity or combativeness, grimacing, mannerisms, posturing, stereotypy, rigidity, echolalia or echopraxia, verbigeration, waxy flexibility and catalepsy (World Health Organization, 2019).

Table 1 - Diagnostic classification of catatonia in ICD and DSM.

Edition (Year)	Nosological category (code)
ICD-9 (1978)	Catatonic type schizophrenia (295.2)
DSM-III (1980)	Schizophrenic Disorder Catatonic Type (295.2)
ICD-10 (1990)	Catatonic schizophrenia (F20.2) Organic catatonic disorder (F06.1)
DSM-IV (1994)	Schizophrenia Catatonic Type (295.20) Catatonic Disorder Due to a General Medical Condition (293.89)
DSM-5 (2013)	Catatonia Associated With Another Mental Disorder (Catatonia Specifier) (293.89) Catatonic Disorder Due to Another Medical Condition (293.89) Unspecified Catatonia (293.89)
ICD-11 (2019)	Catatonia associated with another mental disorder (6A40) Catatonia induced by substances or medications (6A41) Secondary catatonia syndrome (6E69) Catatonia, unspecified (6A4Z)

ICD = International Statistical Classification of Diseases and Related Health Problems, DSM = Diagnostic and Statistical Manual of Mental Disorders.

Catatonia is a neuropsychiatric syndrome with many secondary causes (Carroll et al., 1994; Johnson, 1993; Volle et al., 2021). Although the ICD and the DSM have recognized the diagnosis of secondary catatonia since 1990 and 1994, respectively, this diagnosis is often overlooked. In a 20-year retrospective study of 65 patients admitted with a diagnosis of ICD-9's schizophrenic catatonia, it was found that the prevalence of an organic brain disease explaining catatonic symptoms and signs, doubled from admission (5/65) to discharge (10/65) (Gama Marques, 2020). Epilepsy is a neurological condition that over time has established an area of intersection between neurology and psychiatry (Reynolds & Trimble, 2009). Since the first description that Kahlbaum mentioned that there was a high incidence of organic causes for catatonia, especially epilepsy (Johnson, 1993). Some of the first studies on the relationship between catatonia and epilepsy date back to 1948 when an injection of cerebrospinal fluid (CSF) from patients with catatonic schizophrenia into the cistern of patients with epilepsy was reported to have antiepileptic properties (Poloni, 1948). In 1952, Beluffi published a review in which he studied the relationship between catatonia and epilepsy, considering a likely common structural and pathophysiological origin in the central nervous system, and concluded that the catatonic syndrome should be considered more as having an organic origin in the mesencephalon than a cortical psychic origin (Beluffi, 1952). In 1953, La Porta published a case report and review about catatonic schizophrenia and epilepsy secondary to head trauma (La Porta, 1953). In 1962, while analysing data from the clinical records of patients with schizophrenia who underwent prefrontal lobotomy, Mille identified an apparent association between the diagnosis of catatonic schizophrenia and the development of postsurgical epilepsy (De Mille, 1962) and, after investigating further, he found a statistically significant higher incidence of post-surgical epilepsy in patients with catatonia (De Mille, 1964). In 1964, Vitello reviewed the different types of amphetamine-induced psychosis and published a case report on amphetamine-associated catatonia and epileptic seizures (Vitello, 1964). Kondratenko and Kazakovtsev studied the prognosis of epileptic patients with psychosis with catatonic features and reported that the patients with affective disorders had a better outcome than the ones with epilepsy (Kondratenko & Kazakovtsev, 1986). A seizure is defined as a transient occurrence of symptoms and/or signs due to abnormal excessive or synchronous neuronal activity in the brain (Fisher

et al., 2014). Seizures can be classified as acute symptomatic seizures if a clinical seizure occurs at the time of a systemic insult or in close temporal association with a documented brain insult (Beghi et al., 2010). Epilepsy is a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome (Fisher et al., 2014). The association between catatonia and epileptic seizures does not seem to be a coincidence. The frequency of seizures in patients with catatonia in one case series was almost 14% (Primavera et al., 1994) and another 16% (Barnes et al., 1986), which is higher than in an age-matched general population. Furthermore, epileptic seizures were more common in patients with organic catatonia (Primavera et al., 1994). The relationship between catatonia and epileptic seizures is complex. Some authors hypothesized that catatonia could be a pre-ictal, ictal or post-ictal manifestation (Repchak & Quinn, 2016). It has also been reported that catatonia may mimic Non-Convulsive *Status Epilepticus* (NCSE) (Louis & Pflaster, 1995) and that catatonia and epileptic seizures may overlap, possibly because catatonic stupor predisposes to the development of seizures by decreasing the Gamma-AminoButyric Acid A (GABA-A) receptor activity (Suzuki et al., 2006). Some suggest that because of the rapid response of catatonia to benzodiazepines and electroconvulsive therapy (ECT), it is conceivable that ECT may increase the seizure threshold and that catatonia may be a final manifestation of epileptic activity, with these having a common origin (Luchini et al., 2015). Catatonia is a classic psychiatric syndrome but the identification of its aetiology solely by its clinical manifestations can be difficult. In the case of the association with epileptic seizures, performing an electroencephalogram (EEG) may be the only way to identify them, but even so, it may initially be normal and only be identified after serial or continuous EEGs. Thus, in a patient with catatonia, a high level of suspicion is necessary to identify epileptic seizures, which can influence the therapeutic plan. Therefore, the objective of this review is to summarize the clinical characteristics and management of these patients, looking at epilepsy as a possible cause for catatonia.

Methods

Due to the scarcity of published information on the subject, it was established that all relevant articles with case reports on catatonia, meeting criteria according to the ICD-11, associated with clinical or electroencephalographic evidence of epileptic activity would be included, regardless of the characteristics of the studies, publication date or language. A PubMed search was last performed on 24/12/2021: ((catatoni*[Title]) OR (stupor[Title])) AND (epilep*[Title] OR (ictal[Title]) OR (seizure*[Title]) OR (postictal[Title]) OR (spike-wave[Title])). The full texts or abstracts of all articles were retrieved and assessed for eligibility. Was collected relevant data regarding patients' age, sex, neuropsychiatric history, catatonia manifestations, seizure types, other relevant findings on examination, EEG findings, brain imaging findings, epileptic activity location, most probable aetiology, treatment and remission. These outcomes were defined as follows: neuropsychiatric history as any relevant condition manifesting before the current episode; catatonia manifestations were reported according to the ICD-11 criteria definitions; the seizure types were described according to the 2017 International League Against Epilepsy (ILAE) classification; other relevant findings on examination during the current episode were highlighted; EEG findings were summarized and disturbances were highlighted; brain imaging findings were synthesized and anomalies were emphasized; the location of the epileptic activity was defined by the most likely focus of the epileptic activity based on the EEG or the seizure types; the most probable aetiology that could justify epileptic activity and, therefore, catatonia, or both was reported; the treatment was considered as any intervention performed after an association of catatonia with epileptic activity was found; remission was evaluated as complete when catatonic and epileptic manifestations resolved and the EEG, if available, did not evidenced epileptiform activity; as partial, if all of the above criteria were not met, but the patient improved and, as none if there was no improvement or if it was negligible. Clinical cases were synthesized, focusing on the outcomes described above, the main findings were compiled in a table and results were expressed as percentages. The review was written based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 (Page et al., 2021).

Results

The PubMed search resulted in 81 studies. Of the 81 studies, it was not possible to obtain the reports of 4. The remaining 77 studies were assessed for eligibility: 17 were excluded because did not meet the criteria for catatonia; 5 did not represent cases with epileptic activity; 4 didn't have either of the two; 2 had no temporal association between the two; 13 had no case reports, and 1 was a duplicated case already published in another study included. After screening the titles and abstracts of the list of references from the included articles, 6 additional reports meet the eligibility criteria. Furthermore, one report (Ponte et al., 2020) in which Gama Marques was a co-author was individually selected, assessed for eligibility and added to the review. In the end, 42 reports with 52 case reports were included in the review. The summary of the selection process is represented in a flow diagram in figure 1. After qualitative synthesis of case reports the main findings of the review were summarized in table 2.

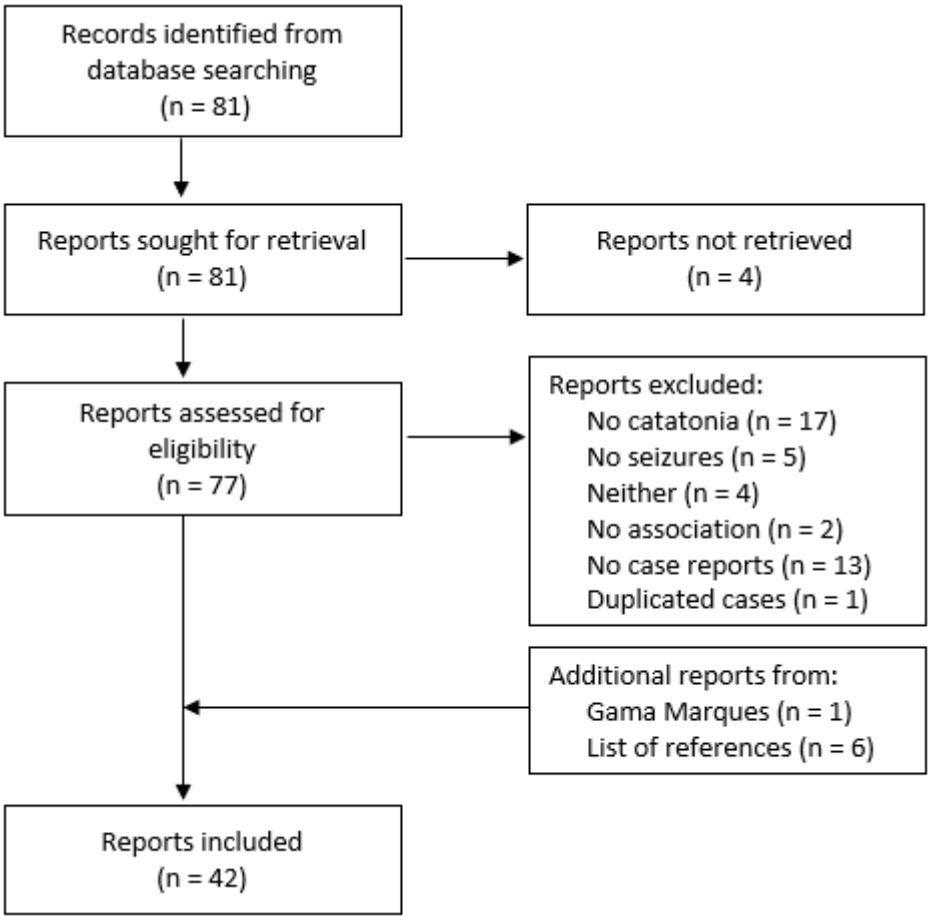

Figure 1 - Flow diagram of studies selection.

Considering the studies included in the review, since 1953 there has been a trend of dispersed publication, with a greater number of publications during the 1980s and again and to a greater extent in recent years after 2013, as evidenced in figure 2. Regarding the origin of the articles, the majority (18) are from the United States of America, followed by Japan (6), England (3) and Italy (3). The rest are single articles from countries in South America, Europe and Asia. The proportion of publications between psychiatric (19) and neurologist (16) authors is similar, but the publication by both (7) is lower.

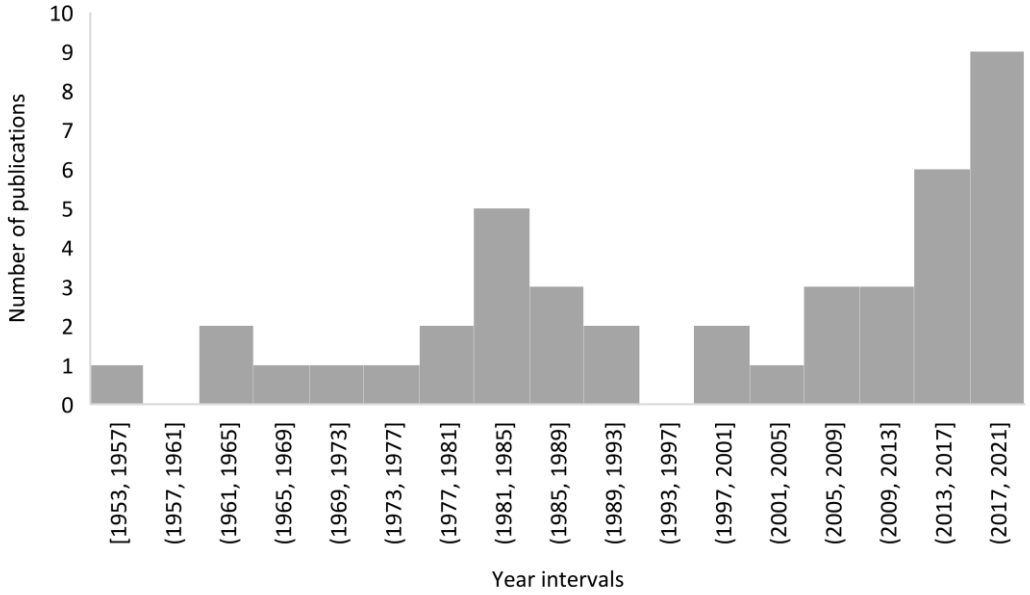

Figure 2 - Publication trend of included articles.

Qualitative synthesis of case reports

La Porta reported the case of a 52-year-old male with a history of head trauma followed by the initiation of epilepsy, presenting with focal aware seizures that was submitted to a trepanation of the skull that resulted in worsened and generalized seizures, and, after the onset of epilepsy, had a psychotic episode. His seizures spontaneously stopped after 31 years and were followed by catatonia, with mutism, catalepsy and stereotypy interrupted with short periods of visual hallucinations and, on observation, he also had bilateral hyperreflexia (La Porta, 1953).

Vitello reported the case of a 26-year-old male, with a recent psychotic episode, who was hospitalized for confusion and psychomotor agitation. He was treated with

electroconvulsive therapy (ECT) and, on non-therapeutic days, he had unknown onset epileptic seizures. When ECT was stopped catatonia emerged and after 3 months an attempted treatment with an amphetamine was tried, which was followed by two unknown onset seizures. When the treatment was stopped, the seizures stopped, but the catatonia worsened, presenting stupor, mutism, rigidity, negativism and grimacing, lasting for three and a half years. After one and a half years asymptomatic, he had a psychotic syndrome, which resolved after 2 years, remaining asymptomatic for 11 years (Vitello, 1964).

Niedermeyer and Khalifeh reported the case of a 12-year-old male, with a history of epilepsy with absence seizures, who was observed for episodes of stupor, mutism and staring, which began at 10 years of age, and which from 11 years of age were accompanied by Generalized Tonic-Clonic Seizures (GTCS). One EEG obtained during one of these episodes showed 2.5-4 Hz generalized spike-wave activity. The patient continued to have them during a 6-year follow-up (Niedermeyer & Khalifeh, 1965).

Thompson and Greenhouse reported the case of a 34-year-old male with a history of epilepsy, who was admitted after having three seizures. During hospitalization, stupor, mutism, staring and catalepsy were detected. Also, a generalized onset seizure and periorbital and mouth twitching were observed. An EEG revealed continuous, bilateral and synchronous irregular slow waves with intermingled multiple spikes. He recovered progressively after receiving phenobarbital and chlordiazepoxide and became asymptomatic on therapy with phenytoin and chlordiazepoxide (Thompson & Greenhouse, 1968).

Thompson and Greenhouse reported a second case of a 61-year-old female with a history of epilepsy, admitted for progressive unresponsiveness. On examination, she presented stupor, mutism, staring, catalepsy and periorbital twitching. An EEG showed continuous, bilateral and synchronous high-voltage 2-3 Hz waves with interspersed multiple spikes. She recovered after treatment with phenobarbital but continued to have epileptic seizures after discharge (Thompson & Greenhouse, 1968).

Smodlaka and Nikolić reported the case of a 40-year-old female with a history of epilepsy who was admitted after five consecutive GTCS. On observation, she had

catatonia with stupor, mutism and staring, and had eyelid twitching. An EEG showed 3 Hz generalized spike-wave discharges. Later, she started to improve and a new EEG showed anterior paroxysmal spike-wave complexes. The next day, the patient clinically recovered and the EEG was almost normal with nonspecific series of 4-5 Hz theta waves (Smodlaka & Nikolić, 1971).

Saper and Lossing reported the case of a 28-year-old female with a history of epilepsy, with bi-monthly episodes of staring and mutism and occasional GTCS, who was brought to the emergency department for a trance state. On observation, she presented catatonia with staring, mutism, catalepsy and echolalia. EEGs showed bilateral synchronous and continuous 3 Hz spike-wave discharges that resolved with diazepam. The patient was medicated with phenytoin, diazepam, trimethadione and primidone, preventing most of the epileptic manifestations (Saper & Lossing, 1974).

Saper and Lossing reported a second case of a 29-year-old male, with a history of head trauma and epilepsy, medicated with phenytoin, primidone and phenobarbital that had recently stopped taking phenytoin and was brought to the emergency room because of confusion and irritability. On observation, he presented mutism, staring, rigidity and 10 to 30 seconds episodes of stupor and posturing. He also had left hyperactive reflexes. An EEG showed continuous and diffuse right-predominant polyspikes and spike-wave discharges. The patient was treated with diazepam and had clinical and electroencephalographic improvement. Antiepileptic medication with phenytoin was restarted, without recurrences (Saper & Lossing, 1974).

Shah & Kaplan reported the case of a 10-year-old female with a history of enuresis, presenting with progressive unresponsiveness, starting with psychomotor slowness, mutism and rigidity, and evolving into a state of stupor, mutism, staring, negativism and waxy flexibility. An EEG demonstrated high voltage bursts of sharp waves, spikes and polyspikes without a specified location reported, and diffuse slowing, but mainly in the left temporal leads. The patient was treated with phenytoin, returning to her baseline state (Shah & Kaplan, 1980).

Rumpl and Hinterhuber reported the case of a 58-year-old male, with a history of bipolar disorder and an episode of catatonia a week after starting amitriptyline that

had started again amitriptyline 2 weeks before and was admitted for severe depression and a stuporous state. On examination, he showed stupor, staring and stereotypy, with periods of verbal perseveration. An EEG showed generalized atypical spike-wave activity and theta and delta slowing that resolved with diazepam, resulting in a resolution of catatonia, after which depressive symptoms became evident. Pneumoencephalography and cerebral scintigraphy showed no abnormal findings. The patient was treated with clonazepam, dibenzepin hydrochloride and oxazepam, with no recurrence of catatonia or seizures. He was discharged on clonazepam and perphenazine, and despite stopping the medication, he remained asymptomatic during a 3-year follow-up (Rumpl & Hinterhuber, 1981).

Drake and Coffey reported the case of a 77-year-old female who was confused and unresponsive after surgery. On observation, she presented periods of stupor, mutism, negativism and catalepsy alternating with grimacing, posturing, eyelid fluttering and automatisms. During the first state, the EEG showed rhythmic theta and delta activity predominant in the right temporal region and, during the second state, it showed epileptiform activity on the left nasopharyngeal lead. A brain computed tomography (CT) showed a mild increase in prominence of the left Sylvian fissure. The patient recovered after phenytoin therapy and the follow-up EEGs only showed mild diffuse slowing (Drake & Coffey, 1983).

Drake and Coffey reported a second case of a 30-year-old female with a history of epilepsy, which became unresponsive, alternating with periods of agitation after surgery. On observation, she presented stupor, mutism, negativism, catalepsy, grimacing and stereotypy alternating with periods of confusion and agitation. During the first state, the EEG had 3.5 Hz spike-wave discharges in the right posterior temporal region with secondary generalization and during the second state it had diffuse slowing with intermittent theta and delta activity. A brain CT had no abnormal findings. After treatment with phenytoin, the patient recovered and the EEG showed only a mild diffuse background slowing. She later had new episodes of behaviour changes, most likely psychogenic seizures (Drake & Coffey, 1983).

Bateman et al. reported the case of a 50-year-old female with a history of a psychotic episode who was admitted due to withdrawal, depression and confusion with a 10-day

evolution. On examination, she exhibited stupor, mutism, and waxy flexibility, and over the next few days began to manifest visual hallucinations and delusions. In the investigation performed, a brain CT had no abnormal findings and an EEG showed generalized atypical spike-and-slow-wave discharges occurring in prolonged runs with brief periods of generalized slow between episodes. The patient was treated with diazepam, with complete clinical and electroencephalographic resolution (Bateman et al., 1983).

Atri and Julius reported the case of a 59-year-old male with a history of alcoholism, stroke and depression treated with maprotiline, who was admitted to the psychiatric service for severe depression. During hospitalization, he continued the treatment with maprotiline and was started on thiothixene. After twelve days, he had an aggravation with generalized weakness, dysphagia and urinary incontinence. At this point, an EEG was performed which did not show abnormal findings. His condition continued to deteriorate, presenting ataxic march and becoming progressively unresponsive until he developed catatonia with stupor, mutism and rigidity, which resulted in the decision to discontinue his medications. A new EEG showed recurrent periodic sharp, slow, and atypical 1.5 Hz spike-wave activity. The patient was treated with diazepam and then phenytoin, normalizing the EEG and returning to his baseline state. A brain CT showed an old infarct in the left parietal region and a new EEG showed only a left temporal slowing. Six months after discharge, an EEG was unremarkable. The authors considered the most likely diagnosis to be the adverse effects of maprotiline (Atri & Julius, 1984).

Lanham et al. reported the case of a 13-year-old female with a history of systemic lupus erythematosus (LSE), who was admitted for psychological withdrawal. On examination, she had mutism, stupor, rigidity, catalepsy and bilateral extension plantar reflexes. In the investigation performed, laboratory results suggested active LSE, a brain CT showed widening of the cortical sulci with small ill-defined non-enhancing low attenuation lesions in the bilateral parietal and temporal regions and an EEG demonstrated bursts of high voltage 1.5-2 Hz spike-and-wave activity in the left frontoparietal region, which normalized with the administration of diazepam. The patient was treated with clonazepam and prednisolone, maintaining controlled

epileptic activity but without a clinical improvement. After increasing the prednisolone dose and receiving a bolus of cyclophosphamide, catatonia improved and the patient recovered completely on maintenance therapy with azathioprine (Lanham et al., 1985).

Dubin et al. reported the case of a 24-year-old female, with a history of a depressive disorder, hospitalized for persistent suicidal ideation. On admission, she presented with a depressive syndrome and, on the third day of hospitalization, she manifested mutism, stupor, posturing and waxy flexibility. An EEG obtain after clinical improvement with haloperidol showed a diffuse slowing and spiking in the temporal region and a brain CT was unremarkable. The diagnosis of temporal lobe epilepsy (TLE) was admitted and the patient was treated with phenytoin, with no recurrence of seizures or catatonia (Dubin et al., 1985).

Lim et al. reported the case of a 55-year-old male with a history of psychotic episodes that had four generalized tonic-clonic seizures, controlled with diazepam before admission. On examination, he had catatonia with staring, mutism, stupor, rigidity and catalepsy. An EEG showed continuous generalized pseudo-periodic sharp waves and spikes discharges and a brain CT had no abnormal findings. The patient was treated with phenytoin, resolving the catatonia and the EEG findings (Lim et al., 1986).

Lim et al. reported a second case of a 67-year-old male with a history of a seizure secondary to head trauma 15 years before, who was admitted for confusion. On the initial evaluation, he presented with mutism, echolalia, perseveration and periods of depressed mood alternating with extreme hyperactivity and combativeness. Later, he developed grimacing, rigidity, posturing and stupor. A brain CT showed minimal diffuse cerebral atrophy and an EEG demonstrated continuous spike-and-wave discharges originating in the right frontocentral region with some spread to the left hemisphere. Afterwards, the patient was treated with phenytoin, resolving the catatonia and a revaluation EEG showed only a mild diffuse slowing (Lim et al., 1986).

Lim et al. reported a third case of a 59-year-old male with a history of focal to bilateral tonic-clonic seizure after abdominal surgery, admitted for episodes of mental confusion. On evaluation, he presented catatonia with mutism, rigidity and catalepsy.

An EEG showed periodic lateralising epileptiform discharges in the left parietal-temporal region and a brain CT demonstrated a mild diffuse cortical atrophy. The patient was treated with phenytoin, with complete resolution of catatonia. A revaluation EEG showed a mild diffuse slowing (Lim et al., 1986).

Kirubakaran et al. reported the case of a 24-year-old male with a history of three hospitalizations for three psychotic episodes with two of them accompanied by catatonia, and four hospitalizations for bizarre behaviour and mutism, during which extensive complementary examinations were performed, including a brain CT scan and multiple EEGs that did not reveal abnormal findings. He also had a history of episodic alcohol abuse and a recent episode of suspected alcohol withdrawal seizures, in which he was medicated with phenytoin but discontinued. In the current hospitalization, the patient was admitted for behavioural changes. On observation, he showed mutism, staring, posturing, waxy flexibility and negativism. To aid in the interview, amobarbital was administered, with a significant improvement of catatonia, which was followed by the development of pressure speech, auditory hallucinations and delusions, with complete remission after haloperidol administration. During hospitalization, after being found on the floor, an EEG was performed which showed bilateral temporal with left side predominance spikes and spike-and-wave complexes. A brain CT showed asymmetry of the ventricles. The diagnosis of TLE was admitted and the patient was treated with carbamazepine. A reassessment EEG had no pathological findings and there was no recurrence of symptoms (Kirubakaran et al., 1987).

Hauser et al. reported the case of a 29-year-old male with a history of viral encephalitis complicated by Generalized Tonic-Clonic *Status Epilepticus* (GTC*SE*), who was admitted for intractable seizures. On the initial evaluation, he had some nonspecific deficits in cognitive functions, nystagmus and ataxia. A brain CT had no abnormal findings and an EEG showed a background slowing with delta and theta activity. Due to suspicion of iatrogenesis, therapy with clorazepate was discontinued, which was followed by two days of GTCS. Then, he started showing stupor, mutism, catalepsy and waxy flexibility. During this period a video EEG with sphenoidal electrodes showed no epileptic activity. The patient was treated with diazepam and therapy with clorazepate was restarted, resolving the catatonia (Hauser et al., 1989).

Hauser et al. reported a second case of a 30-year-old female with a history of seizures and depressive episodes after encephalitis, admitted for intractable seizures. A brain CT and magnetic resonance imaging (MRI) revealed mild cerebral atrophy and an EEG showed a background slowing. Clonazepam therapy was discontinued, followed by an increase in the frequency of focal impaired awareness and focal to bilateral tonic-clonic seizures. After the last seizure, the patient had an episode of auditory hallucinations, delusions, agitation and disorientation that partially responded to treatment with haloperidol. The next day, she presented catatonia with posturing, catalepsy and mutism, maintaining hallucinations and delusions. An EEG showed no epileptic activity. The patient was treated with haloperidol and then lorazepam, resolving the catatonia. There was no recurrence of catatonia and the frequency of seizures returned to its baseline (Hauser et al., 1989).

Walls et al. reported the case of a 40-year-old female, with a history of recurrent episodes of psychotic depression and a previous episode of catatonia, who was admitted for primary depression. On evaluation, she had psychomotor slowness, auditory hallucinations, delusions and intermittent periods of posturing, negativism and mutism. She was enrolled in a study for treatment with nortriptyline and, on day 7 of treatment, she had a focal clonic seizure, followed by stupor, mutism and posturing. An EEG showed a diffuse theta slowing and a brain CT was unremarkable. Nortriptyline was stopped and carbamazepine was started, resulting in complete remission. A new EEG had no pathological findings (Walls et al., 1993).

Nakanishi et al. reported the case of a 34-year-old female, with no relevant history, who was admitted for diminished responsiveness and repeated blinking. On observation, she had episodes of stupor, mutism and staring, suddenly alternating with periods when she followed orders. The laboratory evaluation indicated the presence of idiopathic hypoparathyroidism, an EEG showed continuous generalized 2-4 Hz spike-and-wave complexes with the maximum intensity on frontal lobes, brain imaging studies including radiography, CT and MRI demonstrated the presence of *Hyperostosis Frontalis Interna* (*HFI*) and the compression of the superior medial frontal lobe and Single-Photon Emission Computed Tomography (SPECT) showed diminished circulation and hypometabolism in the superior frontal lobes. The patient was successfully treated

with valproate, ethosuximide and alfacalcidol, normalizing the EEG after administration of the latter (Nakanishi et al., 1990).

Leentjens & Pepplinkhuizen reported the case of a 47-year-old male, with no relevant history, who was admitted to the psychiatric ward for catatonic stupor. On examination, the patient presented mutism, stupor, rigidity, waxy flexibility and staring, interrupted by brief periods of combativeness, echolalia, echopraxia, mannerisms and auditory hallucinations. After discharge, the patient had four more similar episodes monthly. In the complementary exams performed over the first four hospitalizations, no pathological findings were identified, including on brain CT and EEG. During the fifth hospitalization, the patient reported involuntary movements consistent with focal clonic seizures, after receiving an injection of haloperidol and improving his mental state. After that, an EEG with suborbital electrodes showed paroxysms of waves in the prefrontal and frontal areas, superimposed with sharp waves. The diagnosis of frontal lobe epilepsy was admitted and the patient was treated with carbamazepine, having a complete remission and no recurrences up to two years of follow-up. An brain Magnetic Resonance Imaging (MRI) performed after discharge for aetiological investigation showed no abnormal findings (Leentjens & Pepplinkhuizen, 1998).

Kanemoto et al. reported the case of a 78-year-old male, with no relevant history, who was referred for psychiatric evaluation during hospitalization due to episodic mutism alternating with combativeness. In the evaluation, staring, mutism and catalepsy were identified, consistent with catatonia. An EEG showed generalized pseudo-rhythmic 1.5-2 Hz spike-and-wave discharges and a brain CT was unremarkable. The patient was found to have stopped long-term benzodiazepine therapy, so he was restarted on diazepam, resulting in a complete resolution of catatonia and electroencephalographic findings (Kanemoto et al., 1999).

Swartz et al. reported the case of a 68-year-old male with a history of schizoaffective disorder and head trauma that was brought to the hospital for behavioural changes. On admission, therapy with bupropion was increased and, on the first three days of hospitalization, a clinical picture of catatonia with staring, mutism, stupor and negativism was identified. Temporal and spatial disorientation and occasional jerking

movements of his extremities were also reported. The patient was medicated with lorazepam for catatonia, having a significant improvement. An EEG showed generalized sharp and sharp-and-slow-wave activity. As a result, lorazepam therapy was discontinued, resulting in a transient reappearance of catatonia symptoms, which regressed after valproate was initiated and reached therapeutic levels. Until discharge, he had no recurrence of catatonia or seizures (Swartz et al., 2002).

Suzuki et al. reported the case of a 62-year-old female with a history of psychotic episodes, who was admitted for catatonia. On evaluation, she had stupor, mutism, catalepsy, staring and rigidity. During the hospitalization, she had focal impaired awareness seizures and focal to bilateral tonic-clonic seizures, which resolved spontaneously. An EEG showed subclinical seizures beginning with a fast-recruiting activity of low amplitude in the left temporal region and progressive spread to the left frontal region, followed by slow waves and a brain MRI had no abnormalities. Phenytoin administration completely resolved epileptic activity, but catatonia remained until an ECT course was completed (Suzuki et al., 2006).

Suzuki et al. reported a second case of a 56-year-old male with a history of bipolar disorder that during hospitalization for nephrosis developed delirium which resolved with haloperidol administration but was followed by a catatonic syndrome with stupor, mutism, catalepsy, negativism, staring and rigidity. Afterwards, focal clonic seizures with automatism were observed and an EEG showed long bursts of generalized multiple spike-and-wave activities. Brain CT and MRI had no abnormal findings. The patient was initially treated with midazolam and then with phenytoin and diazepam, resolving the seizures, but maintaining the catatonia, which only resolved after ten days (Suzuki et al., 2006).

Suzuki et al. reported a third case of a 67-year-old female, with a history of schizophrenia and recurrent catatonia, admitted for a new episode of catatonia. On examination, she had stupor, mutism, catalepsy, negativism, staring and rigidity. A brain MRI had no abnormalities and an EEG showed recurrent bursts of generalized spike-and-wave discharges, accompanied by generalized clonic seizures. The patient was treated with phenytoin, resolving the epileptic activity, but maintaining catatonia, which improved temporarily on a trial with flunitrazepam but only resolved with ECT.

She remained in remission with maintenance therapy with ECT, lithium and phenytoin (Suzuki et al., 2006).

Gunduz et al. reported the case of a 24-year-old female, with a history of epilepsy, meningitis, and an acute psychotic episode, who was admitted for a month-long catatonia that began after a generalized onset seizure after discontinuation of antiepileptic medication. On observation, she presented stupor, mutism, negativism, mannerisms, rigidity and bilateral extension plantar reflexes. Brain MRI was unremarkable and an EEG showed a high-voltage diffuse right-predominant theta slowing. As she did not respond to therapy with diazepam and haloperidol, the patient was treated with ECT and then with olanzapine due to the onset of visual hallucinations and delusions. One week after discharge, she had a new unknown onset seizure, followed by catatonia. The diagnosis of postictal catatonia was admitted and the patient was treated again with ECT and medicated with sodium valproate, returning to her previous state (Gunduz et al., 2008).

Iseki et al. reported the case of a 32-year-old male with no relevant history, admitted after a headache followed by a generalized convulsion and consciousness disturbance. On observation, he had catatonia with stupor, mutism, staring and catalepsy and also presented nuchal stiffness, automatisms and fever. Because of the suspicion of viral encephalitis, the patient was started on acyclovir, vidarabine and phenytoin. The investigation performed revealed the following results: brain MRI showed T2 and Flow-sensitive Alternating Inversion Recovery (FAIR) high-intensity areas in the cortex and subcortical white matter of the right insula and lateral temporal lobe; a CSF analysis showed moderated pleocytosis with lymphocytosis; a Positron Emission Tomography (PET) brain scan demonstrated a diminished uptake of flumazenil in the right frontotemporal area; a first brain SPECT revealed hypoperfusion of the right frontotemporal region and a second one, performed after a diazepam injection showed normal perfusion; a PET study of the brain with FluoroDeoxyGlucose (FDG) showed a normal glucose metabolism. EEGs performed showed abnormal activity mainly in the frontotemporal region, first with slow and then continuous high amplitude 1-3 Hz rhythmic activities, improving with diazepam administration and followed by a temporarily clinical remission. This led to the initiation of treatment with

lorazepam, but 2 days after he developed quasi-rhythmic movements of the limbs, with an EEG showing an almost continuous 1.1-1.3 Hz periodic pattern on the right frontocentral area and an electromyogram (EMG) revealed left brachioradialis periodic brief contraction, suggesting *Epilepsia Partialis Continua* (*EPC*). After treatment with phenytoin, carbamazepine and lorazepam, the patient had a complete remission (Iseki et al., 2009).

Sahaya and Lardizabal reported the case of a 20-year-old female, with no relevant history, who was admitted for behaviour changes and delusions. During hospitalization, she was found on the floor, lethargic, moaning and unresponsive and later she became stuporous. In the investigation performed, CSF analysis showed lymphocytosis, a brain MRI had no abnormal findings and an EEG demonstrated diffuse theta-delta slowing with two generalized seizures. Due to the suspicion of viral encephalitis, she started empirical therapy with acyclovir, doxycycline and fosphenytoin, but this diagnosis was not confirmed, as the viral serologies were negative. The patient had to be intubated and then had a tracheostomy. During this period several symptoms or signs of catatonia were identified, including stupor, negativism, waxy flexibility and posturing. She also had bilateral extension plantar reflex and ankle clonus. A PET brain scan showed decreased uptake of FDG into bilateral thalamus and occipital lobes and a new EEG demonstrated reactive background and alpha activity in the posterior head regions. The diagnosis of postencephalitic catatonia was assumed and the patient was treated with lorazepam, resolving catatonia. The reassessment EEG was unremarkable and there was no recurrence of catatonia or seizures (Sahaya & Lardizabal, 2010).

Monti et al. reported the case of a 51-year-old female, with a history of Hashimoto's thyroiditis, who was admitted after two GTCS followed by prolonged episodes of stupor, mutism and staring. A brain MRI was unremarkable and a video-EEG showed long-duration seizures recurring every 20-30 min with bifrontal spike-and-wave activity and diffuse irregular 1-2 Hz spikes, polyspikes and waves. Diazepam and valproate were tried without success and interictal visual and auditory hallucinations and delusions were observed. After phenytoin administration, the seizure frequency decreased but did not resolve. Because of the suspicion of an acute encephalopathy,

endocrinology tests were performed, detecting high levels of serum anti-thyroid antibodies. The patient was treated with methylprednisolone and then switched to oral corticosteroids, having a complete clinical and electroencephalographic remission. After two years, she had a recurrence but recovered completely after immunosuppression and remained asymptomatic on maintenance therapy with phenytoin (Monti et al., 2011).

Coffey reported the case of a 21-year-old male, with a history of autism spectrum disorder and intellectual disability, who was hospitalized three times for episodes of self-injurious behaviours refractory to multiple therapies. A brain CT had no abnormal findings and EEG was not performed for safety reasons. In the third hospitalization, an episode of forced vocalizations was observed, followed by a fencing posture, consistent with a focal bilateral motor seizure arising from the frontal lobe. Then, he showed stupor, mutism and stereotyped self-injurious behaviours, which resolved temporarily with the administration of lorazepam. The patient was treated with phenytoin, improving rapidly and returning to his basal state. He had two relapses within six months associated with subtherapeutic levels of phenytoin (Coffey, 2013).

Gélisse and Crespel reported the case of a 24-year-old female with a history of juvenile myoclonic epilepsy and bipolar disorder, that had confusion after discontinuation of clonazepam and introduction of oxazepam, followed by stupor, mutism, staring and myoclonic seizures. The EEG showed continuous irregular bilateral 5-6 Hz spike-and-wave complexes. The patient was administered clonazepam, with complete clinical resolution (Gélisse & Crespel, 2015).

Izuno et al. reported the case of a 26-year-old male with a history of depression, who was admitted for catatonia, presenting with mutism, stupor, negativism, catalepsy, rigidity and staring. An EEG showed frontal spike-and-wave activity and the brain MRI had no abnormal findings. Due to suspicion of frontal lobe epilepsy, carbamazepine and levetiracetam were started, decreasing the spike-and-wave frequency in the EEG, but without clinical response. In a new aetiological investigation performed, an EEG and a long-term video EEG corroborated the previous findings and a brain MRI and the brain SPECT had no relevant findings. Several antiepileptic medications were tried including diazepam, carbamazepine, levetiracetam, valproate and phenobarbital, with

only the last two resulting in electroencephalographic improvement, but without a symptomatic benefit. Suspecting schizophrenia, the antiepileptics were discontinued and aripiprazole was tried, resulting in an improvement of his condition, which prompted the addition of olanzapine. About two months after, a GTCS was observed and valproate was added. After 48 hours, he had a significant improvement of catatonia. Afterwards, a diagnosis of autism spectrum disorder with mild intellectual disability was made. After discharge, he maintained frequent spike-and-wave activity in the EEG but remained asymptomatic (Izuno et al., 2016).

Repchak and Quinn reported the case of a 44-year-old male with a history of epilepsy under treatment, that after abdominal surgery developed catatonia characterized by staring, mutism and stupor, and also bilateral ankle clonus. An EEG demonstrated generalized periodic epileptiform discharges. The patient was treated with a combination of valproate, phenytoin and levetiracetam without improvement and then all medications were stopped and lacosamide was started, having a resolution of catatonia and improvement in the EEG, without recurrences (Repchak & Quinn, 2016).

Repchak and Quinn reported a second case of a 78-year-old male with a history of neuropathy and depression that was medicated with gabapentin plus paroxetine and developed sudden confusion and visual changes that resolved with discontinuation of these medications. However, a week later he was admitted due to an altered state of consciousness. On evaluation, he presented intermittent episodes of catatonia with stupor, mutism, staring, catalepsy, echopraxia, perseveration, negativism interspersed with a normal state of consciousness. An EEG showed intermittent frontal sharp-and-slow-wave discharges and diffuse delta and theta slowing. The discharges were solved with lorazepam and the patient improved. The patient had no response to levetiracetam, which was replaced by phenytoin, resulting in remission of symptoms. The antiepileptic was discontinued after 6 months with no recurrence of catatonia or seizures (Repchak & Quinn, 2016).

Repchak and Quinn reported a third case of a 55-year-old female with a history of bipolar disorder, hospitalized for subarachnoid haemorrhage, identified in brain CT and submitted to aneurysm clipping, which was complicated by meningitis. During hospitalization, a psychiatric evaluation was requested, in which a condition

interpreted as akinetic mutism was identified and treated with pramipexole. The patient was discharged medicated with levetiracetam for seizures prophylaxis and was hospitalized again, after seven days, for ventriculomegaly with transependymal flow on an unspecified brain scan. On examination, she presented with stereotypy, mutism, rigidity, echopraxia, echolalia, perseveration, waxy flexibility and staring. An EEG showed a continuous right frontal epileptogenic cerebral dysfunction, which was solved with lorazepam and fosphenytoin. On revaluation, she maintained waxy flexibility and staring. A video EEG indicated *EPC*, originating in a frontal focus. She did not improve on therapy with the three antiepileptics. Upon discharge, the EEG improved, but the patient remained with mutism, waxy flexibility and tremor (Repchak & Quinn, 2016).

Tan et al. reported the case of a 59-year-old male, with a history of bipolar disorder and recent head trauma that was brought to the hospital for behavioural changes. On admission, he was disorientated and agitated. A brain CT was performed and demonstrated a small left paracentral subarachnoid haemorrhage. During hospitalization he became increasingly unresponsive and, after one week, showed stupor, staring, mutism, rigidity and waxy flexibility. An EEG showed four episodes of electrographic seizures with onset in the right paracentral region with arrhythmic spikes and polyspikes evolving to generalized rhythmic discharges, which resolved with the administration of midazolam. The patient was treated first with phenytoin and valproate and later a benzodiazepine was added resulting in a transient improvement. Due to adverse effects, all previous medications were stopped and levetiracetam was started. The patient returned to his basal state and had no recurrence of catatonia or seizures. At discharge and six months later, the EEGs had no pathological findings (Tan et al., 2016).

Gaete and Velásquez reported the case of a 68-year-old male with a history of depression medicated with venlafaxine, mirtazapine, quetiapine and risperidone, taken to the emergency room due to behavioural changes, a decrease in motor activity and visual hallucinations. On examination, the patient presented mutism, waxy flexibility and rigidity and later developed stupor. An EEG showed generalized slow theta background activity with 1 Hz pseudo-periodic generalized spike and spike-wave

discharges. A brain CT was not significant. Due to the initial suspicion of viral encephalitis, which was not confirmed after CSF analysis, empirical therapy with acyclovir and antiepileptic therapy with valproate were started. Due to the need for invasive ventilation, midazolam was also administered. The patient recovered completely from catatonia and the last EEG performed had no pathological findings (Gaete & Velásquez, 2017).

George and Langford reported the case of an 82-year-old male, with a history of a depressive disorder and a probable head trauma followed by a GTCS, who was brought to the emergency department because of behavioural changes. In the evaluation, intermittent episodes of catatonia were documented, with mutism, negativism, rigidity, echolalia and perseveration, accompanied by complex automatisms, interspersed with a return to his basal mental state. A brain MRI showed a parenchymal volume loss consistent with his age, chronic microangiopathic changes and bilateral lacunar infarcts. An EEG demonstrated a left-predominant bifrontal slowing and two focal onset seizures, coinciding with the catatonic syndrome. The diagnosis of frontal lobe epilepsy was assumed and the patient was treated with levetiracetam and lorazepam, returning to his baseline state. After discharge, he was diagnosed with dementia (George & Langford, 2017).

Quagliato et al. reported the case of a 58-year-old female with a history of febrile seizures and episodes suggestive of absence seizures, taken to the emergency department due to sudden visual, auditory and olfactory hallucinations, with amnesia for the episode. During hospitalization, she had intermittent episodes of auditory and olfactory hallucinations followed by a catatonic syndrome with posturing, mutism and stupor, alternating with a normal mental state. An EEG showed a diffuse abnormal activity, mainly on the left temporal and frontal areas and a brain MRI evidenced a smaller hippocampal volume on left. The most likely diagnosis was TLE and the patient was medicated with oxcarbazepine, having a complete remission (Quagliato et al., 2018).

Verbraeken and Luykx reported the case of a 38-year-old male with a history of epilepsy, non-compliant with antiepileptic medication that was brought to the emergency room due to confusion and reduced awareness. On the initial evaluation,

he had bradyphrenia and amnesia. An EEG showed a general slowing with no seizure pattern and a brain MRI had no abnormal findings. The patient was restarted on valproate and, on the next day, a tonic-clonic seizure was observed. In the following days, he started manifesting catatonia, characterized by stupor, staring, posturing, grimacing, stereotypy, impulsivity and ambitendency. Two EEGs performed during catatonia were unchanged and the diagnosis of postictal catatonia was admitted. The patient was medicated with lorazepam, improved his symptoms and remained symptom-free after discontinuing the medication. At discharge, an EEG showed only short episodes of general slowing (Verbraeken & Luykx, 2018).

Mader et al. reported the case of a 26-year-old male with a history of schizoaffective disorder, catatonia and head trauma, who was brought to the emergency department for suspected epileptic seizures, after discontinuation of therapy with lorazepam. On observation, he had catalepsy, waxy flexibility, stupor, mutism, negativism, rigidity, posturing and bilateral hyperreflexia. During the stay in the emergency department, rhythmic movements of the right leg consistent with a focal clonic seizure were also observed. An EEG demonstrated episodes of 2.5 Hz Generalized Rhythmic Delta Activity (GRDA) alternating with non-GRDA background activity with beta, alpha, theta and rare delta waves. Brain CT and MRI had no abnormal findings. Given the EEG results, lorazepam was administered, which resulted in clinical improvement. The patient was treated with levetiracetam but, due to the recurrence of catatonia, lorazepam was administered again, and because of fluctuation in the state of consciousness, he had to be intubated and administered propofol. Continuous video EEG monitoring showed the onset of some periods of GRDA being accompanied by focal clonic seizures. The EEG anomalies disappeared after 4 days of levetiracetam, lacosamide and propofol. The patient was discharged medicated with levetiracetam and lacosamide. Due to the recurrence of seizures, valproate was added, and after that, no further recurrences of catatonia or seizures were reported (Mader et al., 2020).

Baqir et al. reported the case of a 51-year-old male, with a history of occasional marijuana consumption, moderate alcoholism and head trauma, admitted for psychomotor agitation and aggressive behaviour. Later, he had a fever of 38,2 ºC, that

did not reoccur. In the investigation performed, an EEG revealed occasional intrusions of slowing in the mid-temporal region and brain CT and MRI showed a small left parafalcine and bifrontal subdural hematoma, secondary to a previous traumatic brain injury. On evaluation, the patient had pressured speech, loose associations and racing thoughts, which raised the hypothesis of bipolar disorder and he was treated accordingly. During hospitalization, his level of consciousness started to fluctuate and he exhibited periods of stupor, staring, and mutism. A prolonged EEG documented generalized, monomorphic theta activity and the patient was treated with lorazepam, improving his symptoms and normalizing the EEG pattern. A subsequent EEG showed generalized rhythmic activity, indicating a subclinical seizure. Antiepileptic treatment was progressively increased as EEGs showed generalized epileptic activity, abundant runs of waxing and waning theta activity, and a greater degree of encephalopathy, resulting in a combination of levetiracetam, lacosamide, valproate, topiramate and phenytoin. A generalized tonic-clonic seizure was also detected on a video EEG. The poor response to antiepileptic drugs and the EEG pattern of encephalopathy led the authors to consider the diagnosis of autoimmune encephalitis and empirical treatment with methylprednisolone and immunoglobulin was started. A new EEG was taken, which was described as having less epileptic activity. Near discharge, the EEG showed mild diffuse encephalopathy and probable frontal epileptic activity, but with no definite seizure. On discharge, the patient was asymptomatic and after one month returned to his baseline (Baqir et al., 2020).

Ponte et al. reported the case of a 33-year-old male, with a previous diagnosis of schizophrenia and substance abuse, with a week-long headache, nausea and vomiting, without pathological findings on brain CTs, who was admitted for auditory hallucinations, delusions, insomnia and psychomotor agitation. After administration of haloperidol, the patient began to manifest paroxysmal catatonia, with mutism, negativism, rigidity and catalepsy, which did not resolve with lorazepam. During hospitalization, he had an episode of dysautonomia, respiratory instability and a generalized tonic-clonic seizure. Repeated EEGs revealed a diffuse theta-delta slowing and a brief left frontotemporal electrographic seizure. Brain MRI showed a right fronto-opercular and anterior temporal lesion compatible with head trauma. The

patient was treated with valproate, quetiapine and lorazepam. One month later, anti-N-Methyl-D-Aspartate Receptor (NMDAR) antibodies were detected in the CSF and the diagnosis of anti-NMDAR encephalitis was confirmed. Intravenous immunoglobulin and methylprednisolone were started and then switched to prednisolone and cyclophosphamide. Later, the patient remained medicated with azathioprine and quetiapine. Up to 3 years after discharge, he had no recurrence of catatonia or epileptic seizures (Ponte et al., 2020).

Volle et al. reported a case of a 65-year-old male with a history of obsessive-compulsive disorder, an acute symptomatic seizure secondary to electrolyte abnormalities due to malnutrition and suspected personality disorder traits or autism spectrum disorder (ASD), who was admitted after two generalized tonic-clonic seizures (GTCS). After antiepileptic treatment, there was a clinical and electroencephalographic resolution of the epileptic seizures but he developed catatonia characterized by mutism, negativism, staring and stereotypy. On the examination were also found temporal and spatial disorientation and psychomotor slowness. To investigate the aetiology, a continuous video EEG was performed, which demonstrated multiple subclinical seizures. The EEG tracing showed near-continuous generalized periodic discharges and intermittent spike-wave morphology with evolution into brief to intermediate duration runs of generalized rhythmic delta. The patient was treated with lorazepam with a significant improvement and returned to his baseline state after therapy with levetiracetam (Volle et al., 2021).

Zandifar and Badrfam reported a case of a 61-year-old male, with a history of schizophrenia, admitted for auditory hallucinations and delusions. On the 1st day of hospitalization, he developed lethargy, nausea and sweating, and a seizure was observed, which was controlled with lorazepam. From the investigation, hyponatremia of 120 mg/L, a leucocytosis of 15700/ml and a positive Polymerase Chain Reaction (PCR) test for COronaVirus Disease 2019 (COVID-19) stood out. A brain CT and an EEG did not reveal changes. An intravenous saline solution was started to correct the hyponatremia and, shortly thereafter, he started a clinical picture of catatonia characterized by stupor, mutism, posturing, negativism, rigidity and staring and was

treated with lorazepam. The catatonia resolved and there were no recurrences (Zandifar & Badrfam, 2021).

Somani et al. reported a case of a 35-year-old male who was admitted to the Intensive Care Unit (ICU) after four generalized tonic-clonic seizures, regaining consciousness and having no further seizures after medication with midazolam and valproate. Although the next day, he presented stupor, mutism, staring and negativism, therefore he was medicated with lorazepam, having a significant immediate response. After that, he was maintained on therapy with lorazepam and valproate, having a complete resolution of catatonia. In the investigation, a cavernoma in the right parietal lobe with surrounding haemorrhage was detected on brain CT and MRI. EEG data was not reported. After discharge, lorazepam was discontinued and he continued to be medicated with valproate, without recurrence of catatonia or epileptic seizures (Somani et al., 2021).

Sanada et al. reported the case of a 66-year-old female with a history of bipolar disorder, who was admitted for episodes of impairment of consciousness, suspension of movement and maintenance of posture. On observation, she had stupor, mutism, catalepsy and waxy flexibility. A brain MRI had no abnormal findings and an EEG showed repetitive spikes from the left frontocentral area evolving to bilateral frontal and parietal areas. The patient was treated first with diazepam, with no response, and then with fosphenytoin. Due to the recurrence of catatonia, lorazepam was administered. Then levetiracetam and valproate were started resolving catatonia but maintaining some alteration in consciousness. A new EEG was performed, which showed intermittent 3 Hz GRDA and a PET brain scan showed hypermetabolism in the bilateral frontal and parietal lobes. The EEG and PET brain scan findings normalized and the patient was discharged in complete remission (Sanada et al., 2021).

Table 2 – Main findings of case reports.

Author, year	Age, sex	Neuropsychiatric history	Catatonia findings	Seizure types	Other findings	EEG anomaly	Imaging anomaly	Probable location	Most probable aetiology	Treatment	Remission
La Porta, 1953	52, ♂	Head trauma, epilepsy, psychotic episode	Mut, Cat, Sty	GOS	Visual hallucinations, abnormal DTR	NA	NA	Generalized	Post-traumatic epilepsy	NA	NA
Vitello, 1964	26, ♂	Psychotic episode	Stu, Mut, Rig, Neg, Gri	UOS	None	NA	NA	Unknown	Amphetamine iatrogenesis	NA	Complete
Niedermeyer & Khalifeh, 1965	12, ♂	Epilepsy	Stu, Mut, Sta	GTCS	None	ED	NA	Generalized	Primary epilepsy	NA	None
Thompson & Greenhouse, 1968	34, ♂	Epilepsy	Stu, Mut, Sta, Cat	GOS	Periorbital and mouth twitching	ED	NA	Generalized	Primary epilepsy	CDPX + PB; CDPX + PHT	Complete
	61, ♀	Epilepsy	Stu, Mut, Sta, Cat	None	Periorbital twitching	ED	NA	Generalized	Primary epilepsy	PB	Partial
Smodlaka & Nikolić, 1971	40, ♀	Epilepsy	Stu, Mut, Sta	GTCS	Periorbital twitching	ED	NA	Generalized	Primary epilepsy	NA	Complete
Saper & Lossing, 1974	28, ♀	Epilepsy	Sta, Mut, Cat, Ecl	None	None	ED	NA	Generalized	Primary epilepsy	DZP; DZP + PHT + TMO + PRM	Partial
	29, ♂	Head trauma, epilepsy	Mut, Sta, Rig	None	Abnormal DTR	ED	NA	Generalized	Primary epilepsy	DZP; PHT + PRM + PB	Complete
Shah & Kaplan, 1980	10, ♀	Enuresis	Stu, Mut, Sta, Rig, Wfx, Neg	None	Slowness	ED, slowing	NA	Unknown	Primary epilepsy	PHT	Complete
Rumpl & Hinterhuber, 1981	58, ♂	Bipolar disorder, catatonia	Stu, Sta, Sty	None	Perseverations, depressed mood	ED, slowing	None	Generalized	Amitriptyline iatrogenesis	DZP; CZP + OXP + dibenzepin; CZP + PZ	Complete
Drake & Coffey, 1983	77, ♀	None	Stu, Mut, Neg, Cat, Gri, Pos	None	Periorbital twitching, automatisms	ED, slowing	Prominent fissure	Focal	Unknown	PHT	Complete
	30, ♀	Epilepsy	Stu, Mut, Neg, Cat, Gri, Sty	None	Agitation	ED, slowing	None	Temporal	Primary epilepsy	PHT	Complete
Bateman et al., 1983	50, ♀	Psychotic episode	Stu, Mut, Wfx	None	Visual hallucinations, delusions	ED, slowing	None	Generalized	Unknown	DZP	Complete
Atri & Julius, 1984	59, ♂	Depressive disorder, alcoholism, stroke	Stu, Mut, Rig	None	Depressed mood, dysphagia, ataxia incontinence	ED, slowing	Old infarct	Unknown	Maprotiline iatrogenesis	DZP; PHT	Complete
Lanham et al., 1985	13, ♀	Systemic lupus erythematosus	Stu, Mut, Rig, Cat	None	Abnormal PR	ED	Widening sulci, small lesions	Frontal and parietal	Systemic lupus erythematosus	DZP; CZP + PRED + CTX + AZA	Complete
Dubin et al., 1985	24, ♀	Depressive disorder	Mut, Stu, Pos, Wfx	None	Depressed mood	ED, slowing	None	Temporal	Primary epilepsy	PHT	Complete
Lim et al., 1986	55, ♂	Psychotic episodes	Sta, Mut, Stu, Rig, Cat	GTCS	None	ED	None	Generalized	Unknown	PHT	Complete
	67, ♂	Head trauma, ASS	Mut, Ecl, Ext, Cmb, Gri, Pos, Rig, Stu	None	Depressed mood, Perseverations	ED, slowing	Cerebral atrophy	Frontal	Unknown	PHT	Complete
	59, ♂	ASS	Mut, Rig, Cat	None	None	ED, slowing	Cerebral atrophy	Parietal and temporal	Unknown	PHT	Complete
Kirubakaran et al., 1987	24, ♂	Alcoholism, catatonia, ASS,	Mut, Sta, Pos, Wfx, Neg	None	Pressure speech, delusions, auditory	ED	Asymmetry of ventricles	Temporal	Primary epilepsy	CBZ	Complete

		psychotic episodes			hallucinations						
Hauser et al., 1989	29, ♂	Encephalitis, epilepsy	Stu, Mut, Cat, Wfx	GTCS	Nystagmus, ataxia	Slowing	None	Generalized	Benzodiazepine withdrawal	DZP; clorazepate	Complete
	30, ♀	Encephalitis, epilepsy, depressive disorder	Pos, Cat, Mut	FIAS, FBTCS	Delusions, auditory hallucinations, agitation, disorientation	Slowing	Cerebral atrophy	Focal	Benzodiazepine withdrawal	HLP; LZP	Complete
Nakanishi et al., 1990	34, ♀	None	Stu, Mut, Sta	None	None	ED	HFI, decreased circulation and metabolism	Generalized	Hypocalcaemia	VPA + ESM + alfacalcidole	Complete
Walls et al., 1993	40, ♀	Depressive disorder, catatonia	Post, Neg, Mut, Stu	FCS	Delusions, auditory hallucinations, slowness	Slowing	None	Focal	Nortriptyline iatrogenesis	CBZ	Complete
Leentjens & Pepplinkhuizen, 1998	47, ♂	None	Mut, Stu, Rig, Wfx, Sta, Cmb, Ecl, Ecp, Man	FCS	Auditory hallucinations	ED	None	Frontal	Primary epilepsy	CBZ	Complete
Kanemoto et al., 1999	78, ♂	None	Sta, Mut, Cat, Cmb	None	None	ED	None	Generalized	Benzodiazepine withdrawal	DZP	Complete
Swartz et al., 2002	68, ♂	Schizoaffective disorder, head trauma	Sta, Mut, Stu, Neg	None	Disorientation, extremities twitching	ED	NA	Generalized	Bupropion iatrogenesis	VPA	Complete
Suzuki et al., 2006	62, ♀	Psychotic episodes	Stu, Mut, Cat, Sta, Rig	FIAS, FBTCS	None	ED, slowing	None	Frontal and temporal	Unknown	PHT; PHT + ECT	Complete
	56, ♂	Bipolar disorder	Stu, Mut, cat, Neg, Sta, Rig,	GCS	Automatisms	ED	None	Generalized	Unknown	MDZ; DZP + PHT; PHT	Complete
	67, ♀	Schizophrenia, Catatonia	Stu, Mut, Cat, Neg, Sta, Rig	GCS	None	ED	None	Generalized	Unknown	PHT; FNP; PHT + ECT; PHT + ECT + lithium	Complete
Gunduz et al., 2008	24, ♀	Epilepsy, meningitis, psychotic episode	Stu, Mut, Neg, Man, Rig	GOS, UOS	Visual hallucinations, delusions	Slowing	None	Generalized	Primary epilepsy	DZP + HLP; ECT + OLZ; ECT + VPA	Complete
Iseki et al., 2009	32, ♂	None	Stu, Mut, Sta, Cat	*EPC*	Nuchal stiffness, automatisms, fever	RDA	Cortical and subcortical hyperintensities, decreased flumazenil uptake, hypoperfusion	Frontal and temporal	Viral encephalitis	Acyclovir + vidarabine + PHT; DZP; PHT + CBZ + LZP	Complete
Sahaya & Lardizabal, 2010	20, ♀	None	Stu, Neg, Wfx, Pos	None	Delusions, abnormal PR and DTR	ED, slowing	Decreased FDG uptake	Generalized	Viral encephalitis	LZP	Complete
Monti et al., 2011	51, ♀	Hashimoto's thyroiditis	Stu, Mut, Sta	GTCS	Visual and auditory hallucinations, delusions	ED	None	Frontal	Hashimoto's encephalopathy	DZP; VPA; PHT + corticosteroids	Complete
Coffey, 2013	21, ♂	ASD, ID	Stu, Mut, Sty	FBMS	None	NA	None	Frontal	Primary epilepsy	LZP; PHT	Partial
Gélisse & Crespel, 2015	24, ♀	Epilepsy, bipolar disorder	Stu, Mut, Sta	MS	None	ED	NA	Generalized	Benzodiazepine withdrawal	CZP	Complete
Izuno et al., 2016	26, ♂	Depressive disorder	Mut, Stu, Neg, Cat, Rig, Sta	GTCS	None	ED	None	Frontal	Unknown	CBZ + LEV; DZP + CBZ + LEV; VPA + PB; ARI + OLZ + VPA	Partial
Repchak & Quinn, 2016	44, ♂	Epilepsy	Sta, Mut, Stu	None	Abnormal DTR	ED	NA	Generalized	Primary epilepsy	VPA + PHT + LEV; LCM	Complete
	78, ♂	Depressive disorder, anxiety, neuropathy	Stu, Mut, Sta, Cat, Ecp, Neg	None	Perseverations	ED, slowing	NA	Frontal	Antiepileptic discontinuation	LZP; LEV; PHT	Complete
	55, ♀	Bipolar disorder	Sty, Mut, Rig, Ecp, Ecl, Wfx,	*EPC*	Perseverations	ED	Subarachnoid haemorrhage, ACA aneurysm,	Frontal	Hydrocephalus	LEV + LZP + fPHT	None

			Sta				ventriculomegaly				
Tan et al., 2016	59, ♂	Bipolar disorder, head trauma	Stu, Sta, Mut, Rig, Wfx	None	Disorientation, agitation	ED	Subarachnoid haemorrhage	Frontal and parietal	Subarachnoid haemorrhage	MDZ; PHT + VPA + BZD; LEV	Complete
Gaete & Velásquez, 2017	68, ♂	Depressive disorder	Mut, Wfx, Rig, Stu	None	Visual hallucinations	ED	None	Generalized	Pharmacological iatrogenesis	Acyclovir; MDZ; VPA	Complete
George & Langford, 2017	82, ♂	Depressive disorder, head trauma, ASS	Mut, Neg, Rig, Ecl	None	Automatisms, perseverations	ED, slowing	Lacunar infarcts	Frontal	Brain infarct	LZP + LEV	Complete
Quagliato et al., 2018	58, ♀	Epilepsy	Pos, Mut, Stu	None	Auditory, olfactory, visual hallucinations	Abnormal activity	Hippocampal atrophy	Temporal	Primary epilepsy	OXC	Complete
Verbraeken & Luykx, 2018	38, ♂	Epilepsy	Stu, Sta, Pos, Gri, Sty, Imp, Amb	GTCS	Bradyphrenia, amnesia	Slowing	None	Generalized	Primary epilepsy	LZP	Complete
Mader et al., 2020	26, ♂	Schizoaffective disorder, head trauma, catatonia	Stu, Mut, Cat, Wfx, Neg, Rig, Pos	FCS	Abnormal DTR	RDA	None	Generalized	Benzodiazepine withdrawal	LZP; LEV + propofol + LCM; LEV + LCM + VPA	Complete
Baqir et al., 2020	51, ♂	Alcoholism, head trauma	Sta, Mut, Stu	GTCS	Pressured speech, loose associations, racing thoughts, fever	ED, slowing	Small subdural hematoma	Generalized	Autoimmune encephalitis	LZP; LEV + LCM + VPA + TPM + PHT; mPRED + IVIg	Complete
Ponte et al., 2020	33, ♂	Schizophrenia, drug abuse	Mut, Neg, Rig, Cat	GTCS	Delusions, auditory hallucinations, agitation	ED, slowing	Traumatic lesion	Frontal and temporal	Anti-NMDAR encephalitis	VPA + QTP + LZP; mPRED + IVIg; PRED + CTX; AZA + QTP	Complete
Volle et al., 2021	65, ♂	OCD, ASS, ASD	Mut, Neg, Sty, Sta	GTCS	Disorientation, slowness	ED, RDA	NA	Generalized	Unknown	LZP; LEV	Complete
Zandifar & Badrfam, 2021	61, ♂	Schizophrenia	Stu, Mut, Pos, Neg, Rig, Sta	UOS	Delusions, auditory hallucinations	None	None	Unknown	Hyponatremia	Hyponatremia correction + LZP	Complete
Somani et al., 2021	35, ♂	None	Stu, Mut, Sta, Neg	GTCS	None	NA	Parietal Cavernoma	Generalized	Parietal cavernoma	LZP; LZP + VPA	Complete
Sanada et al., 2021	66, ♀	Bipolar disorder	Stu, Mut, Cat, Wfx	None	None	ED, RDA	Frontoparietal hypermetabolism	Frontal	Unknown	DZP; fPHT; LZP; LEV + VPA	Complete

ACA: anterior cerebral artery; Amb: ambitendency; ARI: aripiprazole; ASD: Autism spectrum disorder; ASS: acute symptomatic seizure; AZA: azathioprine; BZD: benzodiazepine; Cat: catalepsy; CBZ: carbamazepine; CDPX: chlordiazepoxide; Cmb: combativeness; CTX: cyclophosphamide; CZP: clonazepam; DTR: deep tendon reflexes; DZP: diazepam; Ecl: echolalia; Ecp: echopraxia; ECT: electroconvulsive therapy; ED: epileptiform discharges; *EPC*: *epilepsia partialis continua*; ESM: ethosuximide; Ext: extreme hyperactivity; FBMS: focal bilateral motor seizure; FBTCS: focal to bilateral tonic-clonic seizure; FCS: focal clonic seizure; FDG: fluorodeoxyglucose; FIAS: focal impaired awareness seizure; FNP: flunitrazepam; fPHT: fosphenytoin; GCS: generalized clonic seizure; GOS: generalized onset seizure; RDA: Rhythmic delta activity; Gri: grimacing; GTCS: generalized tonic-clonic seizure; HFI: hyperostosis frontalis interna; HLP: haloperidol; ID: intellectual disability; Imp: Impulsivity; IVIg: intravenous immunoglobulin; LCM: lacosamide; LEV: levetiracetam; LZP: lorazepam; Man: mannerisms; MDZ: midazolam; mPRED: methylprednisolone; Mut: mutism; NA: not available; Neg: negativism; NMDAR: N-methyl-D-aspartate receptor; OCD: obsessive-compulsive disorder; OLZ: olanzapine; Sta: staring; OXC: oxcarbazepine; OXP: oxazepam; PB: phenobarbital; PHT: phenytoin; Pos: posturing; PR: plantar reflex; PRED: prednisolone; PRM: primidone; PZ: perphenazine; QTP: quetiapine; Rig: rigidity; Stu: stupor; Sty: stereotypy; TMO: trimethadione; TPM: topiramate; UOS: unknown onset seizure; VPA: valproate; Wfx: waxy flexibility.

Patients' characteristics

In the 52 cases included in this review, the mean age of the patients was approximately 44.9 ± 19.3 years old and 59.6% (31/52) were male. Regarding neuropsychiatric history, 76.9% (40/52) had a psychiatric history, 61.5% (32/52) had a neurological history and 5.8% (3/52) had other conditions with possible neurological implications (Hashimoto's thyroiditis, systemic lupus erythematosus and enuresis). The most common psychiatric conditions were depressive disorders (15.4%; 8/52), psychotic episodes (13.5%; 7/52), bipolar disorder (11.5%; 6/52), catatonia (9.6%; 5/52), substance abuse (7.7%; 4/52), schizophrenia (5.8%; 3/52), schizoaffective disorder (3.8%; 2/52) and autism spectrum disorder (3.8%; 2/52). The most frequent neurological conditions were epilepsy (28.8%; 15/52), head trauma (15.4%; 8/52), acute symptomatic seizures (9.6%; 5/52) and encephalitis (3.8%; 2/52).

Clinical presentation

The most frequent manifestations of catatonia were mutism (94.2%; 49/52), stupor (78.8%; 41/52), staring (57.7%; 30/52), catalepsy (40.4%; 21/52), rigidity (40.4%; 21/52), negativism (36.5%; 19/52), waxy flexibility (23.1%; 12/52) and posturing (21.2%; 11/52). The bar chart in figure 3 compares catatonia findings among the most probable epileptic locations. A little more than half of the patients (51.9%; 25/52) had clinical evidence of epileptic seizures. The most frequent types were generalized tonic-clonic seizures (21.2%; 11/52), focal clonic seizures (5.8%; 3/52), generalized onset seizures (5.8%; 3/52), unknown onset seizures (5.8%; 3/52), generalized clonic seizures (3.8%; 2/52), focal impaired awareness seizures (3.8%; 2/52), *epilepsia partialis continua* (3.8%; 2/52) and focal to bilateral tonic-clonic seizures (3.8%; 2/52). Other main clinical features identified on examination included hallucinations (23.1%; 12/52), delusions (17.3%; 9/52), abnormal reflexes (13.5%; 7/52), subtle ictal phenomena (9.6%; 5/52), perseverations (9.6%; 5/52), automatisms (7.7%; 4/52), depressed mood (7.7%; 4/52), disorientation (7.7%; 4/52), psychomotor slowness (7.7%; 4/52) and agitation (7.7%; 4/52).

Investigation and aetiology

EEGs were performed in 92.3% (48/52) of the cases. Only one EEG was described as being normal, with all the other ones having some abnormal findings (97.9%; 47/48),

including epileptiform discharges (81.3%; 39/48), slowing (41.7%; 20/48) and rhythmic delta activity (8.3%; 4/48). Brain imaging exams were performed in 73.1% (38/52) of the cases and anomalies were found in 47.4% (18/38). The epileptic activity was mainly generalized (50%; 26/52), frontal (17.3%; 9/52) or temporal (7.7%; 4/52). Regarding the most probable aetiology, 30.8% (16/52) were cases of likely primary epilepsy without other identifiable precipitating factors or secondary causes, 23.1% (12/52) were associated with iatrogenesis, due to medication side effects (11.5%; 6/52) or discontinuation (11.5%; 6/52), 25% (13/52) were related to other secondary aetiologies and, in 21.2% (11/52), was not possible to identify a likely cause.

Treatment and remission

Information on treatments was available in 92.3% (48/52) of the cases. The majority of the patients were treated with antiepileptics (79.2%; 38/48), followed by benzodiazepines (64.6%; 31/48), antipsychotics (10.4%; 5/48), immunosuppressants (8.3%; 4/48) and ECT (6.3%; 3/48). The most used antiepileptics were phenytoin (43.8%; 21/48), sodium valproate (27.1%; 13/48), levetiracetam (20.8%; 10/48), carbamazepine (10.4%; 5/48) and phenobarbital (8.3%; 4/48). The most used benzodiazepines were lorazepam (31.3%; 15/48), diazepam (29.2%; 14/48), clonazepam (6.3%; 3/48) and midazolam (6.3%; 3/48). Most improved with antiepileptic treatment (87.5%; 42/48), others with immunosuppression (8.3%; 4/48) or antipsychotics (2.1%; 1/48) and one had no response. Overall, the majority had a complete remission (86.5%; 45/52), 7.7% (4/52) had a partial remission, 3.8% (2/52) had none and in one case was not reported enough information.

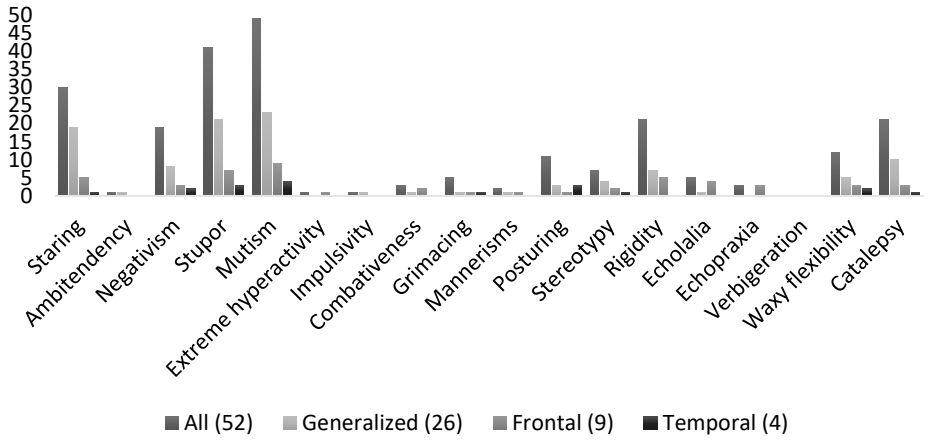

Figure 3 - Frequency of catatonia manifestations according to the epileptic location.

Discussion

The results of this review suggest that most of the patients are adults with a variable age, slightly more males, with a psychiatric history mainly of affective disorders or psychotic episodes and/or a neurological history of epileptic seizures or head trauma. Their clinical presentation consists mostly of features of decreased psychomotor activity with some manifestations of abnormal psychomotor activity and it is common the occurrence of clinical epileptic seizures. When performed, the EEG and the brain imaging exams frequently have abnormal findings. The epileptic activity is mainly generalized and associated with primary epilepsy and most patients have a complete remission after antiepileptic treatment. These findings share some similarities with other published studies on the topic: Repchak et al. (2016) published a systematic review of 17 cases of patients with catatonia secondary to epileptic seizures; Volle et al. (2021) a systematic review of 28 cases of patients with DSM-5 criteria for catatonia and NCSE and Ogyu et al. (2021) a systematic review of 66 cases of patients with BFCRS criteria for catatonia and modified Salzburg Consensus Criteria for NCSE. On those, the mean age and standard deviation were similar, specifically 43.4 ± 21.2 (Repchak & Quinn, 2016), 54.9 ± 15.4 (Volle et al., 2021) and 42.0 ± 22.5 (Ogyu et al., 2021) years old. The proportion of gender was also identical, with a percentage of males of 50% (Repchak & Quinn, 2016), 64% (Volle et al., 2021) and 49% (Ogyu et al., 2021). The frequency of patients with a psychiatric history was lower, in particular 50% (Repchak & Quinn, 2016), 43% (Volle et al., 2021) and 26% (Ogyu et al., 2021). Neurological history was also less common, particularly 57% (Volle et al., 2021) and 39% (Volle et al., 2021), but epilepsy prevalence was similar, with a percentage of 38% in one of the studies (Ogyu et al., 2021). In one report, even though DSM-5 criteria were used, the most frequent manifestations were also primarily of decreased followed by abnormal psychomotor activity, mainly mutism (93%), stupor (89%), negativism (64%), catalepsy (36%) and waxy flexibility (29%) (Volle et al., 2021). In the study reported by Ogyu et al. (2021), patients had a similar frequency of abnormal reflexes of 12%, but a higher incidence of subtle ictal phenomena of 30%. More, in 40% of the cases, the aetiology was related with the occurrence of epileptic seizures in patients with epilepsy and a majority of 77% improved after antiepileptic treatment (Ogyu et al., 2021).

Given our results, some findings that may suggest the presence of epileptic activity in patients with catatonia include a history of epilepsy or traumatic brain injury, consumption of medications that lower the seizure threshold or that are associated with withdrawal syndromes with epileptic seizures, the identification of subtle signs of epileptic activity and, of course, the suspicion or observation of epileptic seizures. If suspicion is raised, an EEG should be performed as soon as possible and epileptic activity should be rapidly controlled. Since almost half of the patients did not have clinical evidence of epileptic seizures and a normal EEG does not definitively rule out the presence of epileptic activity, if suspicion is high, multiple EEGs, continuous monitoring, or the use of special leads such as nasopharyngeal or sphenoidal should be considered. Considering the high prevalence of psychiatric history, it is important to emphasize that a primary cause for catatonia should not be assumed from the outset. In addition to a general complementary assessment, a more or less extensive etiological investigation should be carried out according to the most likely diagnostic hypotheses, which should include at least a brain imaging exam such as a brain MRI, EEG and CSF analysis. As epileptic seizures can be manifested by symptoms or signs commonly associated with psychiatric disorders (Nadkarni et al., 2007; Schmitz, 2005; Slater & Beard, 1963), some previous psychiatric diagnoses were certainly overrepresented, assuming past underlying epileptic activity. Just imagine how many cases of catatonia secondary to epilepsy were not diagnosed before the invention of EEG by Berger in 1924 (Berger, 1929; İnce et al., 2021; Tudor et al., 2005). The same happened for many patients with autoimmune encephalitis such as the anti-NMDAR encephalitis, which was recently described for the first time in 2007 by Dalmau et al. (Dalmau et al., 2007; Marques Macedo & Gama Marques, 2020).

Concerning the evidence included in this work, it is important to note that some of the case reports did not provide enough information to fulfil the different established outcomes. In addition, some, especially the oldest ones, were not reported in a systematic way that addressed the different essential aspects of reporting a case, including patient information, clinical findings, diagnostic course, treatment plan and outcome. As the publication of case reports is important for the understanding of infrequent conditions such as the one that is the subject of this review, it is important

to remember that their writing must be done in a standardized way, following the CAse REports (CARE) guidelines (Riley et al., 2017), to ensure the quality of the information and to allow the cases to be compared with each other so that conclusions can be drawn. Regarding this systematic review, although using PRISMA guidelines, the fact that the search terms were limited to the title, that the search was carried out only in one database and that four studies identified could not be retrieved, may have conditioned that potentially relevant studies were not included. Furthermore, a systematic review of case reports has its limitations due to the type of evidence included, conditioning the ability to establish robust recommendations with an impact on clinical practice. Nonetheless, given the limited amount of information on the subject, we believe that our study can be an important tool to provide a general understanding of the topic.

Regarding the association between catatonia and epileptic activity, when both happened simultaneously, a probable causal relationship could be conceptualized, although that did not happen in every case. In the four in which an EEG was not performed or not reported (Coffey, 2013; La Porta, 1953; Somani et al., 2021; Vitello, 1964), catatonia appeared after the occurrence of clinical epileptic seizures. In these cases, the question remains whether there would be electroencephalographic epileptic activity simultaneously with catatonia. Furthermore, in six cases (Gunduz et al., 2008; Hauser et al., 1989; Verbraeken & Luykx, 2018; Walls et al., 1993; Zandifar & Badrfam, 2021), catatonia appeared after the clinical evidence of epileptic seizures, but it was not possible to identify underlying electroencephalographic epileptic activity during catatonia. In addition, in one case (Sahaya & Lardizabal, 2010), catatonia manifested after electroencephalographic seizures and subsequent EEGs were not significant. In these seven cases, the possibility of an association of catatonia with a postictal state could be raised. This state is known to be associated with psychiatric manifestations mainly psychosis, but catatonia has rarely been reported (Pottkämper & Putten, 2020). More, as was previously mentioned, a single normal routine EEG does not necessarily rule out the presence of epileptic activity, which happened in four of those seven cases. In the remaining three cases there were different approaches that could increase the certainty of the absence of epileptic activity: in the one reported by

Sahaya and Lardizabal (2010), it was performed a continuous EEG monitoring during catatonia; in the one reported by Verbraeken and Luykx (2018) two EEGs were performed before, two more during and one after catatonia and, in the first case reported by Hauser et al. (1989), a video EEG with sphenoidal electrodes was obtained. In this sense, it is important to emphasize that, in addition to a routine EEG, continuous EEG monitoring for at least 24 hours should be requested more often, in order to be able to safely exclude the presence of epileptic activity. Although catatonia has more frequently been reported as an ictal manifestation, it is conceivable that cases of likely postictal catatonia might not be identified and reported if seizures were not observed. On another note, in some cases, it is not clear whether the primary cause is responsible directly for catatonia or indirectly through epileptic seizures. Anti-NMDAR encephalitis is a good example of this, as seizures are a known and frequent manifestation, regardless of the presence of catatonia (Espinola-Nadurille et al., 2019). Furthermore, the absence of improvement of catatonia after adequate seizure control with antiepileptics makes a causal relationship between the two less likely, as it happened in the case of systemic lupus erythematosus where catatonia only resolved after immunosuppressive treatment (Lanham et al., 1985). A similar absence of improvement happened in the three cases reported by Suzuki et al. (2006) and in the case published by Izuno et al. (2016), although in these it was not possible to identify a likely explanation for epileptic activity. Suzuki et al. argued that the cases reported were more likely explained by an occasional and rare overlap between catatonia and epileptic seizures, in patients with a previous psychiatric diagnosis, and that catatonia might predispose to the development of seizures (Suzuki et al., 2006). Izuno et al. defended that in the case reported the retrospective diagnosis of ASD could explain better catatonia than the epileptic discharges on EEG, especially because, although there was an initial electroencephalographic improvement with antiepileptics, later it maintained an abnormal pattern even after clinical remission (Izuno et al., 2016). Lastly, it is relevant to highlight that in three cases (Dubin et al., 1985; Kirubakaran et al., 1987; Leentjens & Pepplinkhuizen, 1998) EEGs showing epileptiform activity were obtained only after improvement of catatonia, which makes it impossible to be sure of its previous presence.

To understand better the relationship with epileptic seizures, it is important to remember the overall pathophysiology of catatonia, which itself is not fully understood. Some evidence from functional brain neuroimaging studies can help us to infer the most likely dysfunctional regions in catatonia. In a recent systematic review (Haroche et al., 2020), which included 137 case reports and 18 group studies, with a total of 186 patients with catatonia in which neuroimaging studies were performed, it was reported that the majority of patients in the case reports demonstrated frontal, temporal or basal ganglia hypoperfusion and that those from the group studies showed emotional dysregulation related to the GABAergic system, with hypoactivation of the orbitofrontal cortex, hyperactivation of the medial prefrontal cortex, and dysconnectivity between frontal and motor areas. Regarding the representativeness, in these clinical cases, it was reported that 77.8% of the patients had an underlying condition that was not considered only psychiatric, however, in group studies, most patients included had an associated diagnosis of schizophrenia and, to a less extent, of affective disorders (Haroche et al., 2020). In a narrative review (Northoff, 2002), a connection between the manifestations of catatonia and the possible brain regions involved was hypothesized. According to the information reported, the motor symptoms seemed to result from an inability to finish movements, which was related to a right posterior parietal dysfunction, important in spatial coordination. The affective symptoms were related mainly to a dysfunction of the medial orbitofrontal cortex, important in emotional processing and modelled by GABAergic transmission, and to a dysfunction in the connections of this region with the premotor and motor cortical areas. Lastly, the behavioural symptoms were related to an inability to inhibit behaviour, arising from a dysfunction of the lateral orbitofrontal cortex and of its glutamatergic connections with the posterior parietal cortex and its connections with the basal ganglia, which could be modulated by dopaminergic receptors D2. According to this, there are cortico-cortical and cortico-subcortical systems involved in the development of catatonia (Northoff, 2002). However, this hypothesis seems insufficient because lesions in other locations can give rise to catatonia and different lesions involving a single one of the areas conceptualized above, produce similar catatonic syndromes. Therefore, it has been proposed that dysfunction in either one of the pathways (cortico-cortical or cortico-subcortical) could lead to catatonia and that

the supplementary motor area could play an additional important role (Haroche et al., 2020). So, based on this, catatonia could arise if epileptic seizures or any other condition causes dysfunction in these or any other key areas of the central nervous system. Furthermore, the effectiveness of medications in the treatment of catatonia may suggest the modulation of certain neurotransmitters in the areas described above, depending on their mechanism of action. Benzodiazepines are a highly effective first-line therapy that modulates GABA-A receptors, which may be hypofunctional in the orbitofrontal (Daniels, 2009; Sienaert et al., 2014) and left sensorimotor cortex (Northoff et al., 1999). Also, catatonia has been reported in patients with anti-GABA-A receptor antibodies (Pettingill et al., 2015; Samra et al., 2020) and, in an experimental study, the cerebroventricular injection in rodents of GABA-A receptor monoclonal Antibodies (mAbs) and Fragment antigen-binding (Fab) fragments induced catatonia and epileptic seizures (Kreye et al., 2021). These receptors play an important role in the development of epileptic seizures (Benarroch, 2021; Treiman, 2001) and are the target of many antiepileptics (Greenfield, 2013). Furthermore, it appears consistent across many studies that patients with catatonia have a higher prevalence of epileptic seizures (Carroll & Boutros, 1995; Carroll et al., 1998; Primavera et al., 1994; Smith et al., 2012), supporting the importance of the hypofunction of GABAergic transmission in catatonia, which may predispose to the development of seizures. Moreover, evidence of the effectiveness of NMDA antagonists in the treatment of catatonia (Beach et al., 2017; Carroll et al., 2007; Theibert & Carroll, 2018) suggests underlying glutamatergic hyperactivity that may involve directly the posterior parietal lobe and indirectly the frontal lobe through GABA-A dysregulation (Daniels, 2009). Additionally, several cases of patients with catatonia secondary to anti-NMDAR encephalitis have been published (Marques Macedo & Gama Marques, 2020) and, in one study, nineteen neuropsychiatric patients with a history of catatonia showed a higher anti-NMDAR antibody immunofluorescence intensity than healthy controls (Lin et al., 2017). Lastly, the role of dopamine is more complex since dopaminergic blockade seems to be associated with an aggravation of catatonia, and the discontinuation of antipsychotics is generally recommended (Sienaert et al., 2014), but partial blockade by some atypical antipsychotics seems to sometimes improve it (Beach et al., 2017; Sienaert et al., 2014; Van Den Eede et al., 2005). Just as antipsychotics that cause greater dopaminergic

blockade can worsen catatonia, they can also induce a neuroleptic malignant syndrome, which could suggest that these two conditions are part of the same disease spectrum (Luchini et al., 2013). More, it has been proposed that this neurotransmitter modulates loops that connect the basal ganglia and the orbitofrontal areas, which are probably regulated by cortical GABAergic transmission (Daniels, 2009). An interesting observation is that some antiepileptics appear to be effective in patients with catatonia without epilepsy, but the level of evidence is low. In a prospective study of patients with lorazepam-refractory DSM-IV catatonia, in a total of nine patients enrolled, carbamazepine was effective in four (Kritzinger & Jordaan, 2001). In addition, it was also reported to be effective in three case reports (Rankel & Rankel, 1988; Spear et al., 1997). Regarding valproate, it was effective in four case reports (Bowers & Ajit, 2007; Krüger & Bräunig, 2001; Yoshida et al., 2005), and the authors of one of the studies reported having effectively treated three more patients (Krüger & Bräunig, 2001). Finally, in a small case series, four patients were reported to have responded to topiramate (McDaniel et al., 2006). It has been proposed that carbamazepine or valproate should be tried in patients with catatonia refractory to conventional therapy and NMDA antagonists (Beach et al., 2017). The therapeutic effect of sodium valproate is thought to be associated with a potentiation of GABAergic transmission, topiramate with glutamatergic antagonism and that of carbamazepine is unclear (Beach et al., 2017). These findings support the pathophysiological considerations discussed above.

The association between catatonia and epileptic seizures is complex and the presence of a causal relationship is not always easy to establish. New prospective cohort studies of patients with catatonia, comparing the ones with epileptic seizures with those without, are needed to better understand this issue and improve outcomes.

Conclusion

Catatonia is a fascinating neuropsychiatric syndrome, about which more and more knowledge has been acquired over time, but about which there is still much to discover. Epileptic seizures are one of its multiple secondary causes, being a phenomenon probably more frequent than one thinks and that needs to be better studied. Its clinical presentation is often nonspecific, so an association with psychiatric

disorders should not be assumed from the outset and any patient with catatonia should be properly investigated to avoid misdiagnosis and ineffective treatments.

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Conflict of Interests

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References

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.).

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Atri, P. B., & Julius, D. A. (1984). Maprotiline hydrochloride associated with a clinical state of catatonic stupor and epileptic encephalogram. *Journal of Clinical Psychopharmacology*, *4*(4), 207–209.

Baqir, H., Cosmo, C., Benevenuto, D., Morar, D., Rizvi, S. A., & Batista, L. M. (2020). Ictal Catatonia in Autoimmune Encephalitis. *Rhode Island Medical Journal (2013)*, *103*(3), 55–58. http://www.ncbi.nlm.nih.gov/pubmed/32236165

Barnes, M. P., Saunders, M., Walls, T. J., Saunders, I., & Kirk, C. A. (1986). The syndrome of karl ludwig kahlbaum. *Journal of Neurology, Neurosurgery and Psychiatry*, *49*(9), 991–996. https://doi.org/10.1136/jnnp.49.9.991

Bateman, D. E., O'Grady, J. C., Willey, C. J., Longley, B. P., & Barwick, D. D. (1983). De novo minor status epilepticus of late onset presenting as stupor. *British Medical Journal (Clinical Research Ed.)*, *287*(6406), 1673–1674. https://doi.org/10.1136/bmj.287.6406.1673-a

Beach, S. R., Gomez-Bernal, F., Huffman, J. C., & Fricchione, G. L. (2017). Alternative treatment strategies for catatonia: A systematic review. *General Hospital Psychiatry*, *48*, 1–19. https://doi.org/10.1016/j.genhosppsych.2017.06.011

Beghi, E., Carpio, A., Forsgren, L., Hesdorffer, D. C., Malmgren, K., Sander, J. W., Tomson, T., & Hauser, W. A. (2010). Recommendation for a definition of acute symptomatic seizure. *Epilepsia*, *51*(4), 671–675. https://doi.org/10.1111/j.1528-1167.2009.02285.x

Beluffi, M. (1952). [Catatonia and epilepsy; primary, secondary and associated catatonia]. *Rivista sperimentale di freniatria e medicina legale delle alienazioni mentali*, *76*(3), 361–379.

Benarroch, E. (2021). What Is the Role of GABA Transporters in Seizures? *Neurology*, *97*(12), 580 LP – 584. https://doi.org/10.1212/WNL.0000000000012574

Berger, H. (1929). Über das Elektrenkephalogramm des Menschen. *Archiv Für Psychiatrie Und Nervenkrankheiten*, *87*(1), 527–570. https://doi.org/10.1007/BF01797193

Bowers, R., & Ajit, S. S. (2007). Is there a role for valproic acid in the treatment of catatonia? In *The Journal of neuropsychiatry and clinical neurosciences* (Vol. 19, Issue 2, pp. 197–198). https://doi.org/10.1176/jnp.2007.19.2.197

Bush, G., Fink, M., Petrides, G., Dowling, F., & Francis, A. (1996). Catatonia. I. Rating scale and standardized examination. *Acta Psychiatrica Scandinavica*, *93*(2), 129–136. https://doi.org/10.1111/j.1600-0447.1996.tb09814.x

Carroll, B. T., Anfinson, T. J., Kennedy, J. C., Yendrek, R., Boutros, M., & Bilon, A. (1994). Catatonic disorder due to general medical conditions. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *6*(2), 122–133. https://doi.org/10.1176/jnp.6.2.122

Carroll, B. T., & Boutros, N. N. (1995). Clinical electroencephalograms in patients with catatonic disorders. *Clinical EEG (Electroencephalography)*, *26*(1), 60–64. https://doi.org/10.1177/155005949502600108

Carroll, B. T., Goforth, H. W., Boutros, N. N., Anfinson, T. J., & Werner, L. (1998). Electroencephalography in Catatonic Disorders Due to General Medical Conditions and Psychiatric Disorders. *CNS Spectrums*, *3*(2), 57–61. https://doi.org/10.1017/S1092852900005551

Carroll, B. T., Goforth, H. W., Thomas, C., Ahuja, N., McDaniel, W. W., Kraus, M. F., Spiegel, D. R., Franco, K. N., Pozuelo, L., & Muñoz, C. (2007). Review of adjunctive glutamate antagonist therapy in the treatment of catatonic syndromes. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *19*(4), 406–412. https://doi.org/10.1176/jnp.2007.19.4.406

Coffey, M. J. (2013). Resolution of self-injury with phenytoin in a man with autism and intellectual disability: the role of frontal lobe seizures and catatonia. In *The journal of ECT* (Vol. 29, Issue 1, pp. e12-3). https://doi.org/10.1097/YCT.0b013e31826cbd8c

Dalmau, J., Tüzün, E., Wu, H., Masjuan, J., Rossi, J. E., Voloschin, A., Baehring, J. M., Shimazaki, H., Koide, R., King, D., Mason, W., Sansing, L. H., Dichter, M. A., Rosenfeld, M. R., & Lynch, D. R. (2007). Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Annals of Neurology*, *61*(1), 25–36. https://doi.org/10.1002/ana.21050

Daniels, J. (2009). Catatonia: clinical aspects and neurobiological correlates. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *21*(4), 371–380. https://doi.org/10.1176/jnp.2009.21.4.371

De Mille, R. (1962). An incidental observation of epilepsy in catatonic schizophrenics after prefrontal lobotomy. *The Journal of Nervous and Mental Disease*, *134*, 182–183. https://doi.org/10.1097/00005053-196202000-00009

De Mille, R. (1964). Epilepsy in catatonic schizophrenics after transorbital leucotomy. *The Journal of Nervous and Mental Disease*, *139*, 393–395.

Drake, M. E. J., & Coffey, C. E. (1983). Complex partial status epilepticus simulating psychogenic unresponsiveness. *The American Journal of Psychiatry*, *140*(6), 800–801. https://doi.org/10.1176/ajp.140.6.800

Dubin, S. E., Kuczmierczyk, A., & Ananth, J. (1985). Catatonic stupor and temporal lobe epilepsy. *Indian Journal of Psychiatry*, *27*(3), 259–261.

Espinola-Nadurille, M., Flores-Rivera, J., Rivas-Alonso, V., Vargas-Cañas, S., Fricchione, G. L., Bayliss, L., Martinez-Juarez, I. E., Hernandez-Vanegas, L. E., Martinez-Hernandez, R., Bautista-Gomez, P., Solis-Vivanco, R., Perez-Esparza, R., Bustamante-Gomez, P. A., Restrepo-Martinez, M., & Ramirez-Bermudez, J. (2019). Catatonia in patients with anti-NMDA receptor encephalitis. *Psychiatry and Clinical Neurosciences*, *73*(9), 574–580. https://doi.org/10.1111/pcn.12867

Fink, M., & Taylor, M. A. (2009). The catatonia syndrome: forgotten but not gone. *Archives of General Psychiatry*, *66*(11), 1173–1177. https://doi.org/10.1001/archgenpsychiatry.2009.141

Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., Engel, J. J., Forsgren, L., French, J. A., Glynn, M., Hesdorffer, D. C., Lee, B. I., Mathern, G. W., Moshé, S. L., Perucca, E., Scheffer, I. E., Tomson, T., Watanabe, M., & Wiebe, S. (2014). ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*, *55*(4), 475–482. https://doi.org/10.1111/epi.12550

Gaete, G., & Velásquez, Á. (2017). [Ictal catatonia presentation as a non-convulsive status epilepticus: A case report]. *Revista medica de Chile*, *145*(1), 126–130. https://doi.org/10.4067/S0034-98872017000100017

Gama Marques, J. (2020). Secondary catatonia: An often overlooked diagnosis. In *Clinical neurology and neurosurgery* (Vol. 196, p. 106012). https://doi.org/10.1016/j.clineuro.2020.106012

Gélisse, P., & Crespel, A. (2015). Mixed myoclonic-absence status epilepticus in juvenile myoclonic epilepsy. *Epileptic Disorders : International Epilepsy Journal with Videotape*, *17*(1), 95–96. https://doi.org/10.1684/epd.2014.0719

George, R., & Langford, A. (2017). Intermittent catatonia and complex automatisms caused by frontal lobe epilepsy in dementia. *BMJ Case Reports*, *2017*, 1–3. https://doi.org/10.1136/bcr-2017-222444

Greenfield, L. J. J. (2013). Molecular mechanisms of antiseizure drug activity at GABAA

receptors. *Seizure*, *22*(8), 589–600. https://doi.org/10.1016/j.seizure.2013.04.015

Gunduz, A., Benbir, G., & Bayar, R. (2008). Postictal catatonia in a schizophrenic patient and electroconvulsive treatment. *The Journal of ECT*, *24*(2), 166–167. https://doi.org/10.1097/YCT.0b013e318150665c

Haroche, A., Rogers, J., Plaze, M., Gaillard, R., Williams, S. C., Thomas, P., & Amad, A. (2020). Brain imaging in catatonia: systematic review and directions for future research. *Psychological Medicine*, *50*(10), 1585–1597. https://doi.org/10.1017/S0033291720001853

Hauser, P., Devinsky, O., Bellis, M., Theodore, W. H., Post, R. M., De Bellis, M., Theodore, W. H., & Post, R. M. (1989). Benzodiazepine withdrawal delirium with catatonic features: Occurrence in patients with partial seizure disorders. *Archives of Neurology*, *46*(6), 696–699. https://doi.org/10.1001/archneur.1989.00520420118033

İnce, R., Adanır, S. S., & Sevmez, F. (2021). The inventor of electroencephalography (EEG): Hans Berger (1873–1941). *Child's Nervous System*, *37*(9), 2723–2724. https://doi.org/10.1007/s00381-020-04564-z

Iseki, K., Ikeda, A., Kihara, T., Kawamoto, Y., Mezaki, T., Hanakawa, T., Hashikawa, K., Fukuyama, H., & Shibasaki, H. (2009). Impairment of the cortical GABAergic inhibitory system in catatonic stupor: a case report with neuroimaging. *Epileptic Disorders : International Epilepsy Journal with Videotape*, *11*(2), 126–131. https://doi.org/10.1684/epd.2009.0257

Izuno, T., Takagi, S., Nakamurai, M., Narushima, K., Uchiyama, T., & Nishikawa, T. (2016). [An Adolescent Case of ASD Presenting with Persistent Catatonia and Epileptic EEG Discharge]. *Seishin shinkeigaku zasshi = Psychiatria et neurologia Japonica*, *118*(3), 125–132.

Johnson, J. (1993). Catatonia: the tension insanity. *The British Journal of Psychiatry : The Journal of Mental Science*, *162*, 733–738. https://doi.org/10.1192/bjp.162.6.733

Kahlbaum, K. L. (1874). *Die Katatonie oder das Spannungsirresein*. Klinische

Abhandlungen über psychische Krankheiten.

Kanemoto, K., Miyamoto, T., & Abe, R. (1999). Ictal catatonia as a manifestation of de novo absence status epilepticus following benzodiazepine withdrawal. *Seizure*, *8*(6), 364–366. https://doi.org/10.1053/seiz.1999.0309

Kirubakaran, V., Sen, S., & Wilkinson, C. B. (1987). Catatonic stupor: unusual manifestation of temporal lobe epilepsy. *Psychiatric Journal of the University of Ottawa : Revue de Psychiatrie de l'Universite d'Ottawa*, *12*(4), 244–246.

Kondratenko, R. P., & Kazakovtsev, B. A. (1986). [Prognostic significance for disability of catatono-delusional and catatonic psychoses in epilepsy patients]. *Zhurnal nevropatologii i psikhiatrii imeni S.S. Korsakova (Moscow, Russia : 1952)*, *86*(6), 825–829.

Kreye, J., Wright, S. K., van Casteren, A., Machule, M.-L., Reincke, S. M., Nikolaus, M., Stöffler, L., van Hoof, S., Sanchez-Sendin, E., Kornau, H.-C., Kaindl, A. M., Wilson, M. A., Greenhill, S., Woodhall, G., Turko, P., Vida, I., Garner, C. C., Wickel, J., Geis, C., … Prüss, H. (2021). Encephalitis patient derived monoclonal GABAA receptor antibodies cause catatonia and epileptic seizures. *BioRxiv*, 2021.01.28.428602. https://doi.org/10.1101/2021.01.28.428602

Kritzinger, P. R., & Jordaan, G. P. (2001). Catatonia: an open prospective series with carbamazepine. *The International Journal of Neuropsychopharmacology*, *4*(3), 251–257. https://doi.org/10.1017/S1461145701002486

Krüger, S., & Bräunig, P. (2001). Intravenous Valproic Acid in the Treatment of Severe Catatonia. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *13*(2), 303–304. https://doi.org/10.1176/jnp.13.2.303

La Porta, F. (1953). [Epileptic syndrome and catatonia caused by cerebral injury]. *Rassegna di neuropsichiatria e scienze affini*, *7*(1), 63–71.

Lanham, J. G., Brown, M. M., & Hughes, G. R. (1985). Cerebral systemic lupus erythematosus presenting with catatonia. *Postgraduate Medical Journal*, *61*(714), 329–330. https://doi.org/10.1136/pgmj.61.714.329

Leentjens, A., & Pepplinkhuizen, L. (1998). A case of periodic catatonia, due to frontal lobe epilepsy. *International Journal of Psychiatry in Clinical Practice*, *2*(1), 57–59. https://doi.org/10.3109/13651509809115116

Lim, J., Yagnik, P., Schraeder, P., & Wheeler, S. (1986). Ictal catatonia as a manifestation of nonconvulsive status epilepticus. *Journal of Neurology, Neurosurgery, and Psychiatry*, *49*(7), 833–836. https://doi.org/10.1136/jnnp.49.7.833

Lin, C.-C., Hung, Y.-Y., Tsai, M.-C., & Huang, T.-L. (2017). Increased serum anti-N-methyl-D-aspartate receptor antibody immunofluorescence in psychiatric patients with past catatonia. *PloS One*, *12*(10), e0187156. https://doi.org/10.1371/journal.pone.0187156

Louis, E. D., & Pflaster, N. L. (1995). Catatonia mimicking nonconvulsive status epilepticus. *Epilepsia*, *36*(9), 943–945. https://doi.org/10.1111/j.1528-1157.1995.tb01639.x

Luchini, F., Lattanzi, L., Bartolommei, N., Cosentino, L., Litta, A., Kansky, C., Mauri, M., Cassano, G. B., Fagiolini, A., & Casamassima, F. (2013). Catatonia and Neuroleptic Malignant Syndrome: Two Disorders on a Same Spectrum? Four Case Reports. *The Journal of Nervous and Mental Disease*, *201*(1). https://doi.org/10.1097/NMD.0b013e31827ab24b

Luchini, F., Medda, P., Mariani, M. G., Mauri, M., Toni, C., & Perugi, G. (2015). Electroconvulsive therapy in catatonic patients: Efficacy and predictors of response. *World Journal of Psychiatry*, *5*(2), 182. https://doi.org/10.5498/wjp.v5.i2.182

Mader, E. C. J., Rathore, S. H., England, J. D., Branch, L. A., & Copeland, B. J. (2020). Benzodiazepine Withdrawal Catatonia, Delirium, and Seizures in a Patient With Schizoaffective Disorder. *Journal of Investigative Medicine High Impact Case Reports*, *8*, 2324709620969498. https://doi.org/10.1177/2324709620969498

Marques Macedo, I., & Gama Marques, J. (2020). Catatonia secondary to anti-N-methyl-D-aspartate receptor (NMDAr) encephalitis: a review. *CNS Spectrums*,

25(4), 475–492. https://doi.org/10.1017/S1092852919001573

McDaniel, W. W., Spiegel, D. R., & Sahota, A. K. (2006). Topiramate effect in catatonia: a case series. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *18*(2), 234–238. https://doi.org/10.1176/jnp.2006.18.2.234

Monti, G., Pugnaghi, M., Ariatti, A., Mirandola, L., Giovannini, G., Scacchetti, S., Nichelli, P., & Meletti, S. (2011). Non-convulsive status epilepticus of frontal origin as the first manifestation of Hashimoto's encephalopathy. *Epileptic Disorders : International Epilepsy Journal with Videotape*, *13*(3), 253–258. https://doi.org/10.1684/epd.2011.0457

Nadkarni, S., Arnedo, V., & Devinsky, O. (2007). Psychosis in epilepsy patients. *Epilepsia*, *48 Suppl 9*, 17–19. https://doi.org/10.1111/j.1528-1167.2007.01394.x

Nakanishi M, S., Neshige, R., Kuroda, Y., & Inoue, Y. (1990). [A case of adult-onset spike-wave stupor associated with hypoparathyroidism and hyperostosis frontalis interna (HFI)]. *Rinsho shinkeigaku = Clinical neurology*, *30*(10), 1114–1117.

Niedermeyer, E., & Khalifeh, R. (1965). Petit mal status ("spike-wave stupor"). An electro-clinical appraisal. *Epilepsia*, *6*(3), 250–262. https://doi.org/10.1111/j.1528-1157.1965.tb03793.x

Northoff, G. (2002). Catatonia and neuroleptic malignant syndrome: psychopathology and pathophysiology. *Journal of Neural Transmission (Vienna, Austria : 1996)*, *109*(12), 1453–1467. https://doi.org/10.1007/s00702-002-0762-z

Northoff, G., Steinke, R., Czcervenka, C., Krause, R., Ulrich, S., Danos, P., Kropf, D., Otto, H., & Bogerts, B. (1999). Decreased density of GABA-A receptors in the left sensorimotor cortex in akinetic catatonia: investigation of in vivo benzodiazepine receptor binding. *Journal of Neurology, Neurosurgery, and Psychiatry*, *67*(4), 445–450. https://doi.org/10.1136/jnnp.67.4.445

Ogyu, K., Kurose, S., Uchida, H., Kanemoto, K., Mimura, M., & Takeuchi, H. (2021). Clinical features of catatonic non-convulsive status epilepticus: A systematic review of cases. *Journal of Psychosomatic Research*, *151*, 110660. https://doi.org/10.1016/j.jpsychores.2021.110660

Page, M. J., Moher, D., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … McKenzie, J. E. (2021). PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*, *372*. https://doi.org/10.1136/bmj.n160

Peralta, V., Cuesta, M. J., Serrano, J. F., & Mata, I. (1997). The Kahlbaum syndrome: a study of its clinical validity, nosological status, and relationship with schizophrenia and mood disorder. *Comprehensive Psychiatry*, *38*(1), 61–67. https://doi.org/10.1016/s0010-440x(97)90055-9

Pettingill, P., Kramer, H. B., Coebergh, J. A., Pettingill, R., Maxwell, S., Nibber, A., Malaspina, A., Jacob, A., Irani, S. R., Buckley, C., Beeson, D., Lang, B., Waters, P., & Vincent, A. (2015). Antibodies to GABAA receptor α1 and γ2 subunits: clinical and serologic characterization. *Neurology*, *84*(12), 1233–1241. https://doi.org/10.1212/WNL.0000000000001326

Poloni, A. (1948). [On the therapeutic effects of the suboccipital injection of catatonic schizophrenic CSF into the cistern of epileptics]. *Rassegna di neuropsichiatria e scienze affini*, *2*(4), 324–327.

Ponte, A., Brito, A., Nóbrega, C., Pinheiro, S., & Gama Marques, J. (2020). Catatonia in Anti-N-Methyl-D-Aspartate (NMDA) Receptor Encephalitis Misdiagnosed as Schizophrenia. *Acta Medica Portuguesa*, *33*(3), 208–211. https://doi.org/10.20344/amp.11077

Pottkämper, J. C. M., & Putten, M. J. A. M. Van. (2020). *The postictal state — What do we know ? November 2019*, 1–17. https://doi.org/10.1111/epi.16519

Primavera, A., Fonti, A., Novello, P., Roccatagliata, G., & Cocito, L. (1994). Epileptic seizures in patients with acute catatonic syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, *57*(11), 1419–1422. https://doi.org/10.1136/jnnp.57.11.1419

Quagliato, L., Piedade, R., Santana, C., & Cheniaux, E. (2018). Catatonia and psychosis

related to epilepsy: A case report. *Clinical Schizophrenia and Related Psychoses*, *12*(3), 142–144. https://doi.org/10.3371/CSRP.QUPI.070816

Rankel, H. W., & Rankel, L. E. (1988). Carbamazepine in the treatment of catatonia. *The American Journal of Psychiatry*, *145*(3), 361–362. https://doi.org/10.1176/ajp.145.3.361

Rao, N. P., Kasal, V., Mutalik, N. R., Behere, R. V, Venkatasubramanian, G., Varambally, S., & Gangadhar, B. N. (2012). Has Kahlbaum syndrome disappeared or is it underdiagnosed? Reexamining the nosology of catatonia. In *The journal of ECT* (Vol. 28, Issue 1, pp. 62–63). https://doi.org/10.1097/YCT.0b013e318223c3f5

Repchak, A. T., & Quinn, D. K. (2016). Epileptic Catatonia: A Case Series and Systematic Review. *Psychosomatics*, *57*(2), 217–225. https://doi.org/10.1016/j.psym.2015.11.007

Reynolds, E. H., & Trimble, M. R. (2009). Epilepsy, psychiatry, and neurology. *Epilepsia*, *50 Suppl 3*, 50–55. https://doi.org/10.1111/j.1528-1167.2009.02039.x

Riley, D. S., Barber, M. S., Kienle, G. S., Aronson, J. K., von Schoen-Angerer, T., Tugwell, P., Kiene, H., Helfand, M., Altman, D. G., Sox, H., Werthmann, P. G., Moher, D., Rison, R. A., Shamseer, L., Koch, C. A., Sun, G. H., Hanaway, P., Sudak, N. L., Kaszkin-Bettag, M., … Gagnier, J. J. (2017). CARE guidelines for case reports: explanation and elaboration document. *Journal of Clinical Epidemiology*, *89*, 218–235. https://doi.org/10.1016/j.jclinepi.2017.04.026

Rumpl, E., & Hinterhuber, H. (1981). Unusual “spike-wave stupor” in a patient with manic-depressive psychosis treated with amitriptyline. *Journal of Neurology*, *226*(2), 131–135. https://doi.org/10.1007/BF00313441

Sahaya, K., & Lardizabal, D. (2010). Catatonia in encephalitis and nonconvulsive seizures: A case report and review of the literature. *Epilepsy and Behavior*, *17*(3), 420–425. https://doi.org/10.1016/j.yebeh.2010.01.008

Samra, K., Rogers, J., Mahdi-Rogers, M., & Stanton, B. (2020). Catatonia with GABA(A) receptor antibodies. *Practical Neurology*, *20*(2), 139–143. https://doi.org/10.1136/practneurol-2019-002388

Sanada, Y., Kajikawa, S., Kobayashi, K., Kuzuya, A., Matsumoto, R., Ikeda, A., & Takahashi, R. (2021). [Non-convulsive status epilepticus manifesting as ictal catatonia: a case report]. *Rinsho shinkeigaku = Clinical neurology*, *61*(6), 385–391. https://doi.org/10.5692/clinicalneurol.cn-001560

Saper, J. R., & Lossing, J. H. (1974). Prolonged trance-like stupor in epilepsy: Petit mal status, spike-wave stupor, spaced-out status. *Archives of Internal Medicine*, *134*(6), 1079–1082. https://doi.org/10.1001/archinte.134.6.1079

Schmitz, B. (2005). Depression and mania in patients with epilepsy. *Epilepsia*, *46 Suppl 4*, 45–49. https://doi.org/10.1111/j.1528-1167.2005.463009.x

Shah, P., & Kaplan, S. L. (1980). Catatonic symptoms in a child with epilepsy. *The American Journal of Psychiatry*, *137*(6), 738–739. https://doi.org/10.1176/ajp.137.6.738

Sienaert, P., Dhossche, D. M., Vancampfort, D., De Hert, M., & Gazdag, G. (2014). A clinical review of the treatment of catatonia. *Frontiers in Psychiatry*, *5*, 181. https://doi.org/10.3389/fpsyt.2014.00181

Slater, E., & Beard, A. W. (1963). The Schizophrenia-like Psychoses of Epilepsy: i. Psychiatric Aspects. *British Journal of Psychiatry*, *109*(458), 95–112. https://doi.org/10.1192/bjp.109.458.95

Smith, J. H., Smith, V. D., Philbrick, K. L., & Kumar, N. (2012). Catatonic disorder due to a general medical or psychiatric condition. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *24*(2), 198–207. https://doi.org/10.1176/appi.neuropsych.11060120

Smodlaka, J., & Nikolić, M. (1971). [Stupor as expression of status epilepticus]. *Neuropsihijatrija*, *19*(3), 179–182.

Somani, A., Sharma, A., Goyal, N., & Gulia, M. (2021). Catatonia associated with seizures due to parietal cavernoma. *Indian Journal of Psychiatry*, *63*(3), 309. https://doi.org/10.4103/psychiatry.indianjpsychiatry_268_20

Spear, J., Ranger, M., & Herzberg, J. (1997). The treatment of stupor associated with

MRI evidence of cerebrovascular disease. *International Journal of Geriatric Psychiatry*, *12*(8), 791–794.

Suzuki, K., Miura, N., Awata, S., Ebina, Y., Takano, T., Honda, T., Shindo, T., & Matsuoka, H. (2006). Epileptic seizures superimposed on catatonic stupor. *Epilepsia*, *47*(4), 793–798. https://doi.org/10.1111/j.1528-1167.2006.00528.x

Swartz, C. M., Bottum, K. M., Salazar Jr, L. S. J., & Salazar, L. S. (2002). Suppression of catatonia-like signs by lorazepam in nonconvulsive status epilepticus without seizure termination. *American Journal of Geriatric Psychiatry*, *10*(3), 348–350. https://doi.org/10.1097/00019442-200205000-00016

Tan, A. H., Low, S. C., Tan, C. Y., Lim, K. S., Tan, C. T., & Lim, S. Y. (2016). "Ictal catatonia": Rare but not to be missed! *Parkinsonism and Related Disorders*, *32*, 137–139. https://doi.org/10.1016/j.parkreldis.2016.09.019

Theibert, H. P. M., & Carroll, B. T. (2018). NMDA antagonists in the treatment of catatonia: A review of case studies from the last 10years. In *General hospital psychiatry* (Vol. 51, pp. 132–133). https://doi.org/10.1016/j.genhosppsych.2017.10.010

Thompson, S., & Greenhouse, A. (1968). Petit Mal Status in Adults. *Annals of Internal Medicine*, *68*(6), 1271–1279. https://doi.org/10.7326/0003-4819-68-6-1271

Treiman, D. M. (2001). GABAergic mechanisms in epilepsy. *Epilepsia*, *42 Suppl 3*, 8–12. https://doi.org/10.1046/j.1528-1157.2001.042suppl.3008.x

Tudor, M., Tudor, L., & Tudor, K. I. (2005). [Hans Berger (1873-1941)--the history of electroencephalography]. *Acta medica Croatica : casopis Hravatske akademije medicinskih znanosti*, *59*(4), 307–313.

Van Den Eede, F., Van Hecke, J., Van Dalfsen, A., Van den Bossche, B., Cosyns, P., & Sabbe, B. G. C. (2005). The use of atypical antipsychotics in the treatment of catatonia. *European Psychiatry : The Journal of the Association of European Psychiatrists*, *20*(5–6), 422–429. https://doi.org/10.1016/j.eurpsy.2005.03.012

Verbraeken, R., & Luykx, J. J. (2018). Persistent catatonia following epileptic seizures: A

case report and systematic literature search. *BMC Psychiatry*, *18*(1), 1–5. https://doi.org/10.1186/s12888-018-1935-0

Vitello, A. (1964). [Amentia with epilepsy-catatonia due to ES-amphetamine]. *Rivista di neurobiologia : organo ufficiale della Societa dei neurologi, neuroradiologi e neurochirurghi ospedalieri*, *10*, 272–292.

Volle, D. C., Marder, K. G., McKeon, A., Brooks, J. O., & Kruse, J. L. (2021). Non-Convulsive Status Epilepticus in the Presence of Catatonia: A Clinically Focused Review. *General Hospital Psychiatry*, *68*(November 2020), 25–34. https://doi.org/10.1016/j.genhosppsych.2020.11.008

Walls, M. J., Bowers, T. C., Dilsaver, S. C., & Swann, A. C. (1993). Catatonia associated with depression secondary to complex partial epilepsy. In *The Journal of clinical psychiatry* (Vol. 54, Issue 2, p. 73).

World Health Organization. (1990). *International statistical classification of diseases and related health problems*. https://icd.who.int/browse10/2019/en

World Health Organization. (2019). *International statistical classification of diseases and related health problems*. https://icd.who.int/browse11/l-m/en

Yoshida, I., Monji, A., Hashioka, S., Ito, M., & Kanba, S. (2005). Prophylactic effect of valproate in the treatment for siblings with catatonia: a case report. In *Journal of clinical psychopharmacology* (Vol. 25, Issue 5, pp. 504–505). https://doi.org/10.1097/01.jcp.0000177850.23534.69

Zandifar, A., & Badrfam, R. (2021). Exacerbation of psychosis accompanied by seizure and catatonia in a patient with COVID-19: A case report. *Psychiatry and Clinical Neurosciences*, *75*(2), 63–64. https://doi.org/10.1111/pcn.13174