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Original Research

The Phenomenology of Anti-NMDA Receptor Encephalitis: A Comparison with "Primary Mental Confusion" in Late 19th Century French Psychiatry

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Abstract

Background: Although various studies have been conducted on anti-NMDA receptor encephalitis since it was first reported in 2007, few studies have closely examined its clinical course. **Methods**: We analyzed 47 case reports of anti-NMDA receptor encephalitis that detailed its clinical course. **Results**: The results of our study supported the clinical course proposed by Iizuka *et al*. **Conclusions**: From the results, it is suggested that the phenomenological features understood as indicative of anti-NMDA receptor encephalitis include: (1) antecedent common cold-like symptoms (31.9%) in the prodromal phase, (2) delirium or acute confusional state (65.9%), (3) symptoms considered to be sudden personality changes (40.4%) in the psychotic phase, (4) central hypoventilation (14.9%) in the unresponsive phase, (5) motor disturbances (57.4%), and (6) autonomic symptoms, mainly without fluctuations (48.9%), in the hyperkinetic phase. These features were found to be similar to "primary mental confusion" (*confusion mentale primitive*) in French psychiatry in the late 19th century. We believe that classical psychiatry can contribute considerably to the interpretation of biological research results.

Keywords: anti-NMDA receptor encephalitis; schizophrenia; phenomenology; history of psychiatry

1. Introduction

In 2007, Dalmau *et al*. [1] identified autoantibodies to anti-NMDA receptors as a cause of encephalitis, establishing the concept of "anti-NMDA receptor encephalitis". Since then, various other autoantibodies have been found to be involved in the development of encephalitis and encephalopathy, and the disease concept of "autoimmune encephalitis" has been proposed [2]. The diagnostic criteria for autoimmune encephalitis were also outlined by Glaus *et al*. in 2016 [3]. Although the clinical picture may vary depending on the type of antibody, psychiatric symptoms are the primary symptoms of many autoimmune encephalitides and are often first examined by psychiatrists [4]. However, anti-NMDA receptor encephalitis differs significantly from common psychiatric disorders, as seizures and central hypoventilation occur in its the clinical course [5]. Immunosuppressive therapy should be the first choice in treatment because early immunosuppressive therapy produces good outcomes [6]. Therefore, psychiatrists should diagnose autoimmune encephalitis as early as possible and provide appropriate treatment.

However, it is not practical to perform invasive tests, particularly lumbar puncture, to confirm the diagnosis in all patients with acute psychiatric symptoms who visit a psychiatric clinic. Furthermore, during periods of severe psychiatric symptoms, tests such as lumbar puncture and electroencephalography, which require the patient to remain at rest, are often difficult to perform. Therefore, it is important to first suspect autoimmune encephalitis based on medical history and symptom evaluation in the psychiatric examination, and then decide whether to proceed with a more invasive examination.

The symptomatology of anti-NMDA receptor encephalitis has already been studied several times [7–10] and referenced in an excellent review by Dalmau *et al*. [11]. These studies are important in identifying the psychiatric symptoms associated with this encephalitis because they include a systematic review of numerous cases. However, for practical use in clinical practice, case reports should be read more thoroughly to determine not only what symptoms were seen but also when and in what order they were seen. The clinical course of anti-NMDA receptor encephalitis was studied by Iizuka *et al*. [5] shortly after its discovery. In particular, their study considers what symptoms appear and in what order they appear in the clinical course of this type of encephalitis. According to Iizuka *et al*. [5], in all four patients examined, the clinical course progressed through five phases: a prodromal phase, psychotic phase, unresponsive phase, hyperkinetic phase, and gradual recovery phase.

According to Iizuka *et al*. [5], in the "prodromal phase", nonspecific cold-like symptoms (e.g., fever, headache, and malaise) associated with the activation of the immune system occur. Subsequently, in the "psychotic phase", the autoantibody related to the tumor acts on the central nervous system, causing psychiatric symptoms—mainly those characteristic of mood disorders and cognitive-behavioral disorders. As for psychiatric symptoms, all four cases they examined showed significant schizophrenia-like or "atypical psychosis"-like [12] symptoms (e.g., disorganized thinking, delusions, hallucinations, and loss of self-awareness). Additionally, symptoms of emotional disturbance (e.g., apathy, lack of emotion, depression, loneliness, and fear) and cognitive decline (e.g., difficulty in using a cellular phone or passing through an automatic ticket gate) were observed in these cases, and all four patients were initially diagnosed with psychiatric disorders. In this psychotic phase, after psychotic symptoms such as hallucinations and delusions occur, generalized convulsions and marked disturbances of consciousness appear, and the patients enter the next phase. In the "unresponsive phase", mutism, akinesia, catalepsy, and muscle rigidity are observed. In the following "hyperkinetic phase", various movement abnormalities—mainly involuntary movements (dyskinesias) of the oral cavity and face—are observed. Various autonomic symptoms also often appear during this period. In the "gradual recovery phase", slow recovery of disturbances of consciousness and involuntary movement are observed [5].

This detailed, clinical-course-focused description of the phenomenology of anti-NMDA receptor encephalitis appears to have not been fully updated. Thus, we analyzed case reports of anti-NMDA receptor encephalitis in which the order of appearance of the symptoms was well described and examined clues to aid in differential diagnosis (especially for differential diagnosis from schizophrenia) by phase.

In the Discussion section, we discuss the phenomenological understanding of anti-NMDA receptor encephalitis. Because this encephalitis is, of course, an organic disease, the psychiatric symptoms that occur in the course of this encephalitis can be considered those of organic psychosis. In classical psychiatry, there have been discussions that attempt to distinguish between the phenomenology of organic and functional psychoses (e.g., schizophrenia) [13]. In fact, the similarity of anti-NMDA receptor encephalitis to Stauder's "lethal catatonia" (*tödliche Katatonie*) syndrome [14] and Mitsuda's "atypical psychosis" [15] has already been noted [12]. In this section, however, we want to focus on the similarity between anti-NMDA receptor encephalitis and "primary mental confusion" (*confusion mentale primitive*) [16,17] in late 19th century French psychiatry.

Primary mental confusion, a concept similar to today's organic psychosis, begins with symptoms like those of the common cold and leads to an acute psychotic state, which includes hallucinations, delusions, and various catatonic symptoms (we will discuss the concept of primary mental confusion in more detail later). Additionally, cases of primary mental confusion were sometimes fatal. In these respects, this concept seems useful in considering the phenomenology of today's anti-NMDA receptor encephalitis. It also seems important to us that French psychiatrists focused on the clinical course of diseases, describing in detail the course of primary mental confusion and discussing phenomenological features useful for differentiating functional from organic psychoses based on this concept.

2. Materials and Methods

At the end of July 2021, we searched for papers on PubMed (https://pubmed.ncbi.nlm.nih.gov/) using the search formula "((“Antibodies” [Mesh]) AND “Anti-N-Methyl-D-Aspartate Receptor Encephalitis” [Mesh]) AND “Receptors, N-Methyl-D-Aspartate” [Mesh]" and found 251 papers. We then examined the idenitifed papers that were fully accessible at the Kyoto University Library Network without any additional costs (105 papers). From those, we found 44 papers in which detailed clinical courses were described. We excluded one paper in Hungarian and another in Chinese because of our linguistic limitations, and we also excluded one paper with an inadequate description of the cases. As a result, 41 papers (including 47 case reports) were obtained [18–58]. These 41 case reports included reports in English and Spanish (Fig. 1).

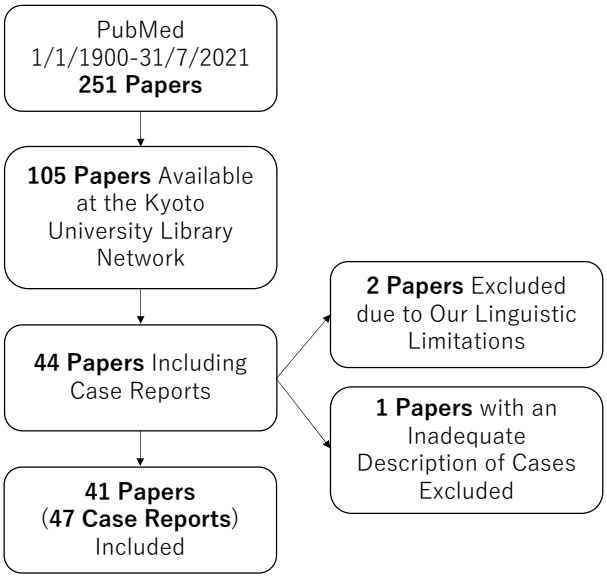

Fig. 1. Selection of case reports.

Subsequently, two evaluators independently listed the symptoms described in each case and identified the order in which each symptom occurred. In counting symptoms,

fever in the prodromal phase was distinguished from hyperthermia as an autonomic symptom in the hyperkinetic phase. Cognitive-behavioral dysfunctions, which can be interpreted as mild disturbances of consciousness, were also distinguished from significant disturbances of consciousness. The symptoms for each phase of the encephalitis are listed and summarized in Tables 1,2. In all cases, we also examined the prevalence of anti-NMDA receptor antibody positivity, EEG abnormalities, and cranial MRI abnormalities.

Additionally, because the recent literature has paid attention to the phenomenological characteristics of anti-NMDA receptor encephalitis in children [59,60] and the elderly [61], we further divided the study into children and adolescents (0–19 years), adults (20–64 years), and the elderly (65 years and older).

3. Results

The mean age of the 47 cases was 26.7 ($\pm$ 17.8) years, the minimum age was 17 months [34], and the maximum age was 77 years [50]. Thirty-seven cases (78.7%) were women. In all cases, 47 (100%) were positive for the anti-NMDA receptor antibodies, 26 (55.3%) had EEG abnormalities, and 16 (34.0%) had cranial MRI abnormalities.

Regarding the clinical course, 41 patients (87.2%) had a course that was consistent with the one outlined by Iizuka *et al.* [5]. Among the other six patients, the hyperkinetic phase preceded the unresponsive phase in four patients [23,26,30,57], and the hyperkinetic phase preceded the psychotic phase in two patients [34,43]. The symptoms described are listed in Table 1 and summarized in Table 2 according to the clinical course of the disease described above (i.e., the prodromal, psychotic, unresponsive, and hyperkinetic phases).

In terms of phenomenological characteristics by age, there were no major differences in the overall trends. However, in children, adolescents, and the elderly, irritability or aggression was common, and as a result, symptoms considered to be sudden personality changes were often observed. In the elderly, common cold-like symptoms were not seen, and delusions were seen in all cases. In children and adolescents, catatonic symptoms and motor disturbances seemed to be more common (however, please note that, due to the small number of these cases, we did not conduct statistical tests).

4. Discussion

4.1 Phenomenological Analysis of the Differential Diagnosis between Anti-NMDA Receptor Encephalitis and Schizophrenia

The results of our study support the clinical course proposed by Iizuka *et al.* [5]. As mentioned in the introduction, the differentiation of anti-NMDA receptor encephalitis from schizophrenia (or brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, and other psychotic disorders) is often problematic. In this study, psychotic symptoms (e.g., auditory hallucinations, visual hallucinations, and delusions) were also frequently observed. Catalepsy, stupor, mutism, and echolalia, which were previously thought to be subtypes of schizophrenia, were also observed.

The final differential diagnosis between encephalitis and schizophrenia can only be made by antibody tests and findings clearly suggestive of organic diseases. However, from the viewpoint of phenomenology, there appear to be indications that anti-NMDA receptor encephalitis should be suspected in each phase.

4.1.1 Prodromal Phase

First, the presence of common cold-like symptoms (e.g., fever, headache, and malaise) in the prodromal phase should raise suspicion of organic diseases. However, from this study, it has also been suggested that these cold-like symptoms may be less likely to be seen in the elderly.

4.1.2 Psychotic Phase

Second, the psychotic phase may be the most important for differential diagnosis. Although Iizuka *et al.* [5] referred to this period as the "psychotic" phase, it may be more appropriate to refer to it as the "psychiatric symptom phase", since this phase includes many psychiatric symptoms other than psychotic symptoms (e.g., hallucinations and delusions). It is expected that patients who present with a substantial proportion of psychiatric symptoms during this phase will be more likely to see a psychiatrist or be hospitalized. Therefore, it is necessary to suspect anti-NMDA receptor encephalitis as early as possible.

During this psychotic phase, encephalitis can be suspected if symptoms such as seizures or (significant) disturbance of consciousness are present. Additionally, it is noteworthy that in 65.9% of cases, there were findings that could be considered mild disturbances in attention and awareness, such as mild disturbance of consciousness, memory impairment, and attention deficit. These findings suggest that delirium or an acute confusional state [62] is common in anti-NMDA receptor encephalitis, which may be a point of differentiation from schizophrenia. This is because previous studies comparing the psychosis of delirium with that of schizophrenia have found that in delirium, delusions tend to involve themes related to the patient's environment and circumstances, and hallucinations are often more visual than auditory [13,63]. Additionally, behaviors and expressions that are difficult to understand as connected to the patient's past personality (and are therefore considered to be sudden personality changes), such as irritability or aggression and abnormal behavior, may also be suggestive of encephalitis. It is possible that children, adolescents, and the elderly are more likely to show symptoms considered to be sudden personality changes, but with the limited number of cases in this study, it is not possible to say for sure.

Table 1. List of symptoms in the prodromal, psychotic, unresponsive, and hyperkinetic phases.

Symptoms in each phase		Total (n = 47)	0–19 years old (n = 14)	20–64 years old (n = 30)	≥65 years old (n = 3)
A. Prodromal phase					
	Fever	14 (29.8%)	4 (28.6%)	10 (33.3%)	0 (0.0%)
	Headache	12 (25.5%)	1 (7.1%)	11 (36.7%)	0 (0.0%)
	Malaise	1 (2.1%)	0 (0.0%)	1 (3.3%)	0 (0.0%)
	Dizziness	1 (2.1%)	0 (0.0%)	1 (3.3%)	0 (0.0%)
B. Psychotic phase					
	Seizures	29 (61.7%)	7 (50.0%)	20 (66.7%)	2 (66.7%)
	(Significant) disturbances of consciousness	7 (14.9%)	2 (14.3%)	4 (13.3%)	1 (33.3%)
	(Mild) disturbances of consciousness	21 (44.7%)	4 (28.6%)	16 (53.3%)	1 (33.3%)
	Memory impairment	11 (23.4%)	1 (7.1%)	8 (26.7%)	2 (66.7%)
	Attention deficit	8 (17.0%)	5 (35.7%)	3 (10.0%)	0 (0.0%)
	Auditory hallucination	6 (12.8%)	2 (14.3%)	4 (13.3%)	0 (0.0%)
	Visual hallucination	8 (17.0%)	3 (21.4%)	4 (13.3%)	1 (33.3%)
	Other hallucinations	1 (2.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)
	Delusion	13 (27.7%)	3 (21.4%)	7 (23.3%)	3 (100%)
	Irritability or aggression	19 (40.4%)	10 (71.4%)	6 (20.0%)	3 (100%)
	Abnormal behavior	14 (29.8%)	2 (14.3%)	12 (40.0%)	0 (0.0%)
	Emotional instability	13 (27.7%)	5 (35.7%)	7 (23.3%)	1 (33.3%)
	Insomnia	9 (19.1%)	8 (57.1%)	1 (3.3%)	0 (0.0%)
	Anxiety	6 (12.8%)	2 (14.3%)	4 (13.3%)	0 (0.0%)
	Fatigue or loss of energy	5 (10.6%)	4 (28.6%)	1 (3.3%)	0 (0.0%)
	Regression	3 (6.4%)	2 (14.3%)	1 (3.3%)	0 (0.0%)
	Coprolalia	1 (2.1%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
C. Unresponsive phase					
	Mutism	12 (25.5%)	6 (42.9%)	6 (20.0%)	0 (0.0%)
	Catalepsy	8 (17.0%)	3 (21.4%)	4 (13.3%)	1 (33.3%)
	Stupor	6 (12.8%)	1 (7.1%)	4 (13.3%)	1 (33.3%)
	Echolalia	3 (6.4%)	1 (7.1%)	2 (6.7%)	0 (0.0%)
	Central hypoventilation	7 (14.9%)	2 (14.3%)	5 (16.7%)	0 (0.0%)
D. Hyperkinetic phase					
	Involuntary movement or dyskinesia	20 (42.6%)	7 (50.0%)	12 (40.0%)	1 (33.3%)
	Motor impairment	14 (29.8%)	7 (50.0%)	7 (23.3%)	0 (0.0%)
	Hyperthermia	10 (21.3%)	1 (7.1%)	8 (26.7%)	1 (33.3%)
	Hyperventilation	3 (6.4%)	1 (7.1%)	2 (6.7%)	0 (0.0%)
	Nausea	6 (12.8%)	2 (14.3%)	4 (13.3%)	0 (0.0%)
	Constipation	2 (4.3%)	2 (14.3%)	0 (0.0%)	0 (0.0%)
	Dysuria	5 (10.6%)	2 (14.3%)	3 (10.0%)	0 (0.0%)
	Increased salivation	2 (4.3%)	0 (0.0%)	2 (6.7%)	0 (0.0%)
	Decreased salivation	1 (2.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)
	Diaphoresis	4 (8.5%)	1 (7.1%)	3 (10.0%)	0 (0.0%)
	Tachycardia	11 (23.4%)	5 (35.7%)	6 (20.0%)	0 (0.0%)
	Bradycardia	1 (2.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)
	Mydriasis	2 (4.3%)	1 (7.1%)	1 (3.3%)	0 (0.0%)
	High blood pressure	2 (4.3%)	2 (14.3%)	0 (0.0%)	0 (0.0%)
	Low blood pressure	2 (4.3%)	1 (7.1%)	1 (3.3%)	0 (0.0%)
E. Other symptoms					
	Anorexia	4 (8.5%)	3 (21.4%)	1 (3.3%)	0 (0.0%)
	Hyperarousal	1 (2.1%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
	Dysgeusia	1 (2.1%)	0 (0.0%)	1 (3.3%)	0 (0.0%)
	Aphasia	4 (8.5%)	2 (14.3%)	2 (6.7%)	0 (0.0%)
	Nuchal rigidity	2 (4.3%)	0 (0.0%)	2 (6.7%)	0 (0.0%)
	Photophobia	1 (2.1%)	0 (0.0%)	1 (3.3%)	0 (0.0%)
	Dysarthria	2 (4.3%)	1 (7.1%)	1 (3.3%)	0 (0.0%)
	Imbalance	1 (2.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)
	Pathologic reflex	1 (2.1%)	0 (0.0%)	1 (3.3%)	0 (0.0%)

Table 2. Summary of symptoms in the prodromal, psychotic, unresponsive, and hyperkinetic phases.

Summary of symptoms in each phase	Total (n = 47)	0–19 years old (n = 14)	20–64 years old (n = 30)	≥65 years old (n = 3)
A. Prodromal phase				
Common cold-like symptoms	15 (31.9%)	4 (28.6%)	11 (36.7%)	0 (0.0%)
B. Psychotic phase				
Findings that strongly raise suspicion of encephalitis or organic psychosis	31 (65.9%)	8 (57.1%)	21 (70.0%)	2 (66.7%)
Mild disturbances in attention and awareness	31 (65.9%)	9 (64.3%)	20 (66.7%)	2 (66.7%)
Psychotic symptoms	20 (42.6%)	5 (35.7%)	12 (40.0%)	3 (100%)
Symptoms considered to be sudden personality changes	19 (40.4%)	10 (71.4%)	6 (20.0%)	3 (100%)
C. Unresponsive phase				
Catatonic symptoms	18 (38.3%)	7 (50.0%)	10 (33.3%)	1 (33.3%)
Central hypoventilation	7 (14.9%)	2 (14.3%)	5 (16.7%)	0 (0.0%)
D. Hyperkinetic phase				
Motor disturbances	27 (57.4%)	10 (71.4%)	16 (53.3%)	1 (33.3%)
Autonomic symptoms	23 (48.9%)	8 (57.1%)	14 (46.7%)	1 (33.3%)

Common cold-like symptoms include fever, headache, and malaise. Findings that strongly raise suspicions of encephalitis or organic psychosis include seizures and (significant) disturbances of consciousness. Mild disturbances in attention and awareness include (mild) disturbance of consciousness, memory impairment, and attention deficit. Psychotic symptoms include auditory hallucinations, visual hallucinations, other hallucinations, and delusion. Symptoms considered to be sudden personality changes include irritability or aggression and abnormal behavior. Catatonic symptoms include mutism, catalepsy, stupor, and echolalia. Motor disturbances include involuntary movement, dyskinesia, and motor impairment. Autonomic symptoms include hyperthermia, hyperventilation, nausea, constipation, dysuria, increased salivation, decreased salivation, diaphoresis, tachycardia, bradycardia, mydriasis, high blood pressure, and low blood pressure (see Table 1).

4.1.3 Unresponsive Phase

In the unresponsive phase, catatonic symptoms (e.g., mutism, catalepsy, stupor, echolalia, and central hypoventilation) are observed. Although catatonic symptoms are also observed in schizophrenia, central hypoventilation has been described as one of the "probable" symptoms in the diagnostic criteria for anti-NMDAR encephalitis [11]. It is possible that age is related to the frequency of these symptoms, but further study would be required to obtain more detailed information.

4.1.4 Hyperkinetic Phase

In the hyperkinetic phase, motor disturbances (e.g., involuntary movement, dyskinesia, and motor impairment) and various autonomic symptoms occur. Although the catatonic cases in the classic monograph by Kahlbaum [64] also show lingual and orofacial dyskinesias, which are common in anti-NMDA receptor encephalitis [11], whether these were catatonic syndromes due to organic diseases such as anti-NMDA receptor encephalitis cannot be ascertained today.

During this hyperkinetic phase, autonomic symptoms were observed in 48.9% of the cases. However, autonomic symptoms may also be observed in schizophrenia. For example, many autonomic symptoms are described as "central-vegetative disturbances" (*zentral-vegetative Störungen*) in the list of "basic symptoms" (*Basissymptome*), a phenomenological concept on schizophrenia by Huber *et al*. [65]. However, while most of the autonomic symptoms of anti-NMDA receptor encephalitis occur after the onset of psychotic symptoms, the autonomic symptoms of schizophrenia are often already observed in its prodromal phase, which can be a point of differentiation between the two conditions. In addition, Huber *et al*. [65] found that the autonomic symptoms as the subtypes of basic symptoms were characterized by a fluctuation between an increase and decrease (e.g., tachycardia and bradycardia). However, in this study, such fluctuating autonomic symptoms were observed in only one of the 23 patients. This may also be the key to distinguishing anti-NMDA receptor encephalitis from schizophrenia.

4.1.5 Summary of Phenomenological Features

From the above discussion, it was suggested that the phenomenological features that should be more indicative of anti-NMDA receptor encephalitis include: (1) antecedent common cold-like symptoms in the prodromal phase, (2) delirium or an acute confusional state, (3) symptoms considered to be sudden personality changes in the psychotic phase, (4) central hypoventilation in the unresponsive phase, (5) motor disturbances, and (6) autonomic symptoms, mainly without fluctuations, in the hyperkinetic phase.

4.2 Historical Analysis: On the Similarity between Anti-NMDA Receptor Encephalitis and "Primary Mental Confusion"

It may seem surprising that a recently discovered disease with these phenomenological features is so similar to the "primary mental confusion" (*confusion mentale primitive*) described more than 120 years ago by Philippe Chaslin [16,17] (1857–1923), a French psychiatrist. In pre-Chaslin classical psychiatry, it was common to regard confusion (*Verwirrtheit*) as secondary to hallucinations and delusions, as discussed by Theodor Meynert [66] (1833–1892), or as a form of melancholia, as discussed by Jules Baillarger [67] (1809–1890). In contrast, Chaslin redefined "primary" (i.e., not secondary to hallucinations and delusions) and melancholy-independent confusion as a syndrome in his 1892 paper [16] and 1895 monograph [17] (see Berrios [68] for details).

Chaslin's primary mental confusion, the concept of a syndrome roughly equivalent to symptomatic or organic psychosis, was at the time thought to result from causes such as infection, typhus, erysipelas, and cerebral rheumatism. According to him, the process of primary mental confusion is as follows [17]: The latent period (*période d'incubation*) lasts from hours to days and includes headache, dizziness, fatigue, strange and inexplicable sensations, dysorexia, dyspepsia, insomnia, anxiety, alternation of irritability, agitation, and apathy. It is also noted that patients are often aware of their bizarreness and complain of difficulty in thinking and memory impairment. The onset (*début*) that occurs after the latent period begins with sudden excitation, which leads to a state of mania or acute psychosis (*délire aigu*). In some cases, there is an irregular alternation of excitation and stupor (i.e., fluctuating catatonia). However, the central pathology is confusion with disorientation, and hallucinations and delusions occur in some cases but not in others. In the complete form (*forme complete et moyenne*), sudden violent behaviors, involuntary movements (e.g., stereotypy), and repeated use of words are especially likely to occur. Excitement is accompanied by (mainly visual) hallucinations and delusions, particularly with erotic, grandiose, variable, and transient characteristics [17].

The clinical course of primary mental confusion varies and can result in (1) rapid or slow recovery, (2) confusion that persists for several years and creates lasting intellectual deficits, (3) dementia, and (4) death. Although some deaths have been described as being caused by pneumonia, it is possible that some primary mental confusion cases died of central hypoventilation due to anti-NMDA receptor encephalitis.

In his famous 1895 clinical lecture [69], Jules Seglas (1856–1939), a psychiatrist from Chaslin's era, examined the distinction between acute paranoia (*paranoia aiguë*, now considered to be related to schizophrenia or delusional disorder) and Chaslin's primary mental confusion. According to Seglas, mental confusion is secondary to hallucinations and delusions in acute paranoia. However, in primary mental confusion, it is "mental confusion which constitutes the fundamental essential disturbance of the affection, while delusions and the hallucinations which result from it are only unstable, secondary symptoms" [69]. Seglas' view is also useful today when examining patients with acute psychosis. In other words, autoimmune encephalities, such as anti-NMDA receptor encephalitis, and other organic psychiatric disorders should be suspected in cases in which delirium or an acute confusional state precedes hallucinations and delusions (i.e., where mental confusion is primary) [70].

Of course, anti-NMDA receptor encephalitis is not easily diagnosed by referring to the concept of primary mental confusion and determining whether a patient is in an "acute confusional state". In fact, the symptoms and clinical courses of this encephalitis are so complex that, in addition to primary mental confusion, other classical psychiatric concepts must be consulted to further refine our concept of the disease; for example, the following concepts could be considered: "atypical psychosis" [12,15], exogenous reaction types (*exogenen Reaktiontypen*) [71], transient syndrome (*Durchgagnssyndrom*) [68], cycloid psychosis (*zykloide Psychosen*) [72], and *bouffée délirante* [73].

5. Conclusions

In this paper, the phenomenological features and clinical courses of anti-NMDA receptor encephalitis were examined across 47 cases. We also described some features that enable early differential diagnosis, especially between schizophrenia and anti-NMDA receptor encephalitis. We have highlighted that the concept of primary mental confusion in late 19th century French psychiatry is similar to what is known as anti-NMDA receptor encephalitis in our time.

However, because of the limited number of articles used in this paper, we could not examine as many cases as in previous studies; thus, further systematic and non-retrospective studies are necessary. Another limitation of this study is that we were not able to collect a sufficient number of cases involving children and the elderly. In recent years, the clinical features of anti-NMDA receptor encephalitis in children [59,60] and the elderly [61] have become increasingly well understood. However, since no clear conclusion on the relationship between age and phenomenology has been reached, an exhaustive age-specific phenomelogical evaluation will be needed in the future.

Recently, the viewpoint that emphasizes the involvement of the NMDA receptor in schizophrenia has been taken seriously [74], and anti-NMDA receptor encephalitis may offer many suggestions on the pathology of schizophrenia. In that case, however, the same attention should be paid to the difference between anti-NMDA receptor encephalitis and schizophrenia, as discussed in this

paper. In this sense, we believe that classical psychiatry can make a considerable contribution to the interpretation of biological research results.

Author Contributions

TM designed the research study. RK and RT performed the research. RK and RT analyzed the data. RK and TM wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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