Case Report: Three Case Reports of Rapidly Progressive Dementias and Narrative Review

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Abstract
Rapidly progressive dementia (RPD) is a heterogeneous group of diseases characterized by cognitive impairment and other neurological disorders developed in a short span of fewer than 2 years. Currently viewed as new and infrequent entities, most medical personnel have little understanding of it. Nevertheless, they significantly compromise many patients’ quality of life. Here, we drive 3 clinical cases that evolve as RPD with different etiologies. \textbf{Case 1:} 70-year-old woman presented to the emergency with neuropsychiatric syndrome for 18 days. The researchers identified inflammatory cerebrospinal fluid (CSF), protein 14-3-3-positive T-tau protein, MRI: T2 and FLAIR hyperintensities in bilateral caudate nuclei with diffusion restriction, EEG shows a generalized periodic pattern with triphasic wave morphology. \textbf{Case 2:} 29-year-old man with cognitive impairment and faciobrachial dystonia seizure. The diagnosis was confirmed by achieving elevated antibodies against voltage-gated potassium channels. \textbf{Case 3:} A 49-year-old woman with encephalopathy and myoclonic seizures; EEG and MRI showed subtle changes. The patient also had a normal CSF but a positive CBA serologic
NMDA-R antibody test. We described fundamental aspects of RPD to allow made differential diagnoses in patients with cognitive impairment and encephalopathy. Establishing an early and accurate diagnosis can benefit patients with RPD etiologies that are treatable and even reversible, decreasing in morbidity and mortality.

Introduction

Dementia is a syndrome of organic nature, in which there is a progressive and global deterioration of previously acquired functions, which interfere with independent execution of daily life activities. Fifty million people are affected worldwide, of which, 60% approximately are from low- and middle-income countries (https://www.who.int/dementia). The usual clinical presentation of dementia is of slow progressive impairment (several years) that results in irreversible changes. However, this can have an acute or subacute presentation (months, weeks, or even days), giving rise to what we know as rapidly progressive dementia (RPD) [1]. This clinical syndrome lacks a conclusive definition other than the period in which the manifestations develop, so it requires a broad differential diagnosis in which etiologies like tumors, metabolic, infectious, inflammatory, autoimmune, prion, vascular, neurodegenerative, and primary diseases are considered. Initially, there may be confusion elucidating the precise cause of encephalopathy; perhaps the clinical screening and clinical course becoming vital for the diagnosis [2].

According to literature, 20–30% of patients are refractory to medical management, and a considerable number of these patients are those whose etiology remains unknown [1]. Although science development gives us tools to approach RPD, it is important to highlight certain aspects. Autoimmune encephalitis has undergone a revolution in the last 10 years in which a large number of antigens and antibodies play a critical role. This is how it has been possible to accurately characterize a series of clinical entities, which has favored the diagnostic and therapeutic approach of these pathologies [3]. Regarding RPD associated with prion diseases such as Creutzfeldt-Jakob disease (CJD) or neurodegenerative diseases such as Alzheimer's disease, it is essential to mention that they present a clinical overlap with a large number of highly treatable disorders. However, they respond in a limited way to treatment. Biochemical studies have verified this. Similar proteins are involved in the pathophysiology of neurodegenerative diseases (such as tau, β-amyloid, -synuclein, among others) described in both Alzheimer’s and prion diseases [4].

Diagnostic criteria for possible autoimmune encephalitis: (1) subacute onset (rapid progression in less than 3 months) of working memory deficit (short-term memory loss), altered mental status, or psychiatric symptoms. In addition, (2) at least one of the following: (A) new focal CNS findings, (B) seizure not explained by a previously known disorder, (C) CFS pleocytosis (white blood cell count of more than 5 cells per mm³ or oligoclonal bands), (D) MRI with finding suggestive of encephalitis (T2 hyper signal lesions and restriction on diffusion sequence). (3) Reasonable exclusion of alternative causes [4].

Case Presentation

Case 1

A 70-year-old female arrived at the emergency room with a chief complaint of crying episodes; depression; incoherent language; a tendency to mutism, apathy, and visual hallucinations for
18 days. She was on the antidepressant drug but did not feel better and re-entry for suspected autoimmune encephalitis cerebrospinal fluid (CSF): protein 14-3-3-positive T-tau protein: 6,772 pg/mL (0–1,149 pg/mL) (Quest/Nichols Institute, Valencia), MRI: T2 and FLAIR hyperintensities in bilateral caudate nuclei with diffusion restriction (Fig. 1a), EEG showing a generalized periodic pattern with triphasic wave morphology (Fig. 1b). She received multiple treatment schemes with steroids and plasmapheresis; no improvement was seen. The patient finally died 3 months later.

**Case 2**

Twenty-nine-year-old male patient with memory loss, disorientation, and marked drowsiness. Subsequently, he presents faciobrachial dystonic seizures at a frequency of more than forty times per hour. He was evaluated several times at a different medical center with normal EEG and brain MRI findings. He was on antipsychotic treatment for schizophrenia without improvement. The patient was taken to the Hospital San José presenting multiple faciobrachial dystonic seizures, remarkable autoimmune epilepsy mediated by antibodies against potassium channels. Screening for infectious and neoplastic diseases as differential diagnosis were made. Brain MRI was normal, and continuous monitoring EEG was performed, see (Figure 2). Multiple episodes of faciobrachial dystonic seizures were evidenced per hour accompanied by a rapid attenuation of the trace, more generalized activity during and after the episodes.

The clinical diagnosis of faciobrachial dystonic seizures was confirmed by achieving elevated antibodies against voltage-gated potassium channels (824 pmol/L) and a positive serologic test for inactive leucine-rich glioma 1 (anti-LGI1). Methylprednisolone was started at a 1 g/day dose for 5 days with no improvement. Plasmapheresis was initially administered throughout ten sessions, with subsequent significant improvement in symptoms. He was also
given cyclophosphamide, which was switched to rituximab due to persistent seizures. The seizures were treated and resolved with rituximab. He has some delays in processing information and problems with divided and sustained visual attention.

**Case 3**

A previously healthy 49-year-old woman experienced working memory loss, disorientation, inappropriate behavior, structured visual hallucinations, and myoclonic seizures, which progressively increased to epileptic encephalopathy. Infectious and neoplastic causes were ruled out. The patient underwent an EEG for 12 h, which showed continuous attenuation with no good sleep patterns and fast activity overlapping bilateral frontal intermittent slowing complex (extreme delta brushes [EDBs]). (Fig. 3a).

An immunological cause was confirmed by employing a brain MRI showing an inflammatory process, described as hyperintense lesions in T2 over the suitable basal nuclei with restricted diffusion images (Figure 3b–e). The patient also had a normal CSF but a positive CBA serologic NMDA-R antibody test.

She was administered 1 g methylprednisolone pulses for 5 days with slight improvement. She then was treated with plasmapheresis for five sessions and subsequently azathioprine 50 mg twice a day. Currently, she has no seizures and showed significant improvement in cognitive domains.

**Discussion**

It has been well mentioned that RPDs are pathologies challenging to diagnose, which delays the beginning of timely treatment. Considering literature findings, 20–30% of patients with autoimmune RPD etiology are refractory to medical management. Of these, a considerable number remain as an RPD of unknown etiology.

An autoimmune mechanism produces approximately 12% of RPDs. The most frequent are those generated by antibodies against the voltage-gated potassium channel complex (VGKC), which comprise 56% of cases. These include antibodies against inactive leucine-rich glioma
1 (LG11) and the contactin-associated simile protein-2 (Caspr2). In addition, the following would be those that involve antibodies against glutamic acid decarboxylase (GAD65) at 22%. Finally, the RPD cases related to antibodies against brain proteins expressed N-methyl-D’ Aspartate receptors (NMDAR) with a prevalence of approximately 3% [5].

Regarding CJD, it is a fatal neurodegenerative encephalopathy. Product of a mutation of prion proteins [6], it is responsible for approximately 62% of RPD in the Memory and Aging Center of the University of California in San Francisco, 13% of RPD cases at the Major Dementia Reference Center in Greece, and 68% at the US National Prion Disease Pathology Surveillance Center. Therefore, it is crucial to make an early diagnosis because it leads to pronounced mental deterioration, movement disorders, blindness, coma, and high mortality rates (90%) [7].

A positive 14-3-3 protein is associated with the diagnostic approach’s rapidly progressing cognitive deterioration. Therefore, this test has been the subject of debate in the management of patients with CJD. Initial studies showed that the test had high sensitivity (92%) and specificity (~80%) if applied in an appropriate clinical setting, generally characterized by a condition such as the one presented by the patient [8, 9].
In EEG, a generalized periodic pattern with triphasic wave morphology is reported, which are conditions with a minor frequency of appearance in other pathologies [9]. Wave complexes with triphasic and periodic morphology are characteristic of CJD [10], and it is estimated that they can be found in approximately 60–90% of patients [11]. Although different patterns have been reported in CJD, the triphasic wave pattern is the most frequent. Still, others such as acute periodic slow-wave complexes (PSWC) can be found, which refer to an epileptiform pattern in the EEG with a sensitivity of 66% and a specificity of 74% [12].

In the exposed clinical case, a picture of acute onset’s cognitive deterioration is displayed at the beginning of the eighth decade of life. According to the literature, people with CJD tend to manifest rapidly progressing dementia, usually around the sixth or seventh decade of life. However, the incidence of late-onset cases has been increasing recently. Likewise, the average age at the onset of the disease is usually around 57–89 years [13].

Another aspect to consider is that, as evidenced in Table 1, RPDs are multifactorial entities in which a broad differential diagnosis is considered. Initially, nonspecific symptoms such as fatigue, instability, dizziness, decreased activity, anxiety, depression, visual disturbances, and memory disturbances may appear. However, emotional predominance symptoms are present in the case, so it is initially approached and managed as a depressive condition without a satisfactory response to treatment [14].

Another finding is the tau protein at 6,772 pg/mL, significantly above the reference values. Regarding this aspect, the literature has shown that the determination of tau protein levels in CSF is a valuable marker for the laboratory diagnosis of CJD. High values of this paraclinical exam with a cut-off point of 1,300 pg/mL have a diagnostic sensitivity of 94%, a specificity of 90%, and a positive predictive value of 92% [15].

It is worth noting that significantly elevated tau protein levels are associated in patients with 14-3-3-positive protein by immunoblot bands. This is evidenced in the case described above [16, 17].

In MRI studies with T2 and FLAIR, the main finding is bilateral hyperintensities in caudate nuclei and diffusion restriction. Hyper signal of the caudate nucleus, the putamen, the cortex, and DWI-weighted restriction images has been reported in approximately 80% of cases [18].

Even though our patient was not genotyped, we consider that she presents with a CJD consistent with an MM genotype due to the manifestation of behavioral symptoms, visual and language alterations present in 54%, 50%, and 61% of the cases, respectively [19].

Regarding the approach and management established in the case presented, an RPD of autoimmune etiology was thought of, and immunomodulatory management was considered due to the benefits of the therapy since there were no paraclinical findings to suspect CJD (tau protein and 14-3-3). The nonresponse to immunotherapy was what increased the suspicion of this disease [20].

When it comes to VGKC antibody encephalopathy, it should be considered that previously, epitopes of the channel itself were considered the target of antibodies. Still, it is currently known that most of these targets the inactivated protein-1 of the glioma rich in leucine (LGI1) and the contacting-associated protein-2 (Caspr2) [16, 17, 20]. In this sense, the LGI1 protein is a secreted neuronal protein that interacts at the presynaptic level with ADAM 23 and postsynaptic with ADAM 22, forming a trans-synaptic complex. Other complex components include presynaptic subunits Kv1.1 and Kv1.2 and the postsynaptic AMPA receptor, which are affected by mutations in the gene code for LGI1. This mechanism decreases AMPA receptor activity in inhibitory neurons [21] and increases glutamate release [22], triggering alterations in memory and epilepsy, as evidenced in the case presented.

Epidemiologically, there is a predominance of the male gender approaching the sixth decade of life. However, cases ranging from the pediatric population to the elderly in the eighth decade have been reported [20].
| Disease                                      | Start | Demographic characteristics | Clinical features                                                                 | NMR                          | CSF                            | Other tests                      | Treatment                                                                 |
|----------------------------------------------|-------|----------------------------|-----------------------------------------------------------------------------------|------------------------------|--------------------------------|----------------------------------|----------------------------------------------------------------------------|
| Vascular                                    |       |                            |                                                                                   |                              |                                |                                  |                                                                             |
| Multi-infarct vascular dementia             | ACE   | Over 50 years of age and at risk of vascular disease | Progressive cognitive decline, accompanied by localized visual, motor, and sensory signs | Multiple hyperintense regions in T2/FLAIR vascular regions | No diagnosis                   | Secondary prevention, treatment of risk factors, and acetylcholinesterase inhibitors |
| Dementia due to strategic heart attack      | TO    | Over 50 years of age and at risk of vascular disease | Sudden onset of cognitive decline and memory loss                                  | Infarcts in the territory of the anterior and posterior cerebral arteries in the hippocampus, thalamus, and angular gyrus | No diagnosis                   | Secondary prevention, treatment of risk factors, and high doses of intravenous corticosteroids |
| Inflammatory cerebral amyloid angiopathy    | S     | Older than 40 years and affects men and women equally | Subacute cognitive impairment, headache, and seizures                               | Microbleeds on T2, large confluent hyperintense lesions on T2 (hypointense on T1) | Could show pleocytosis and elevated proteins | Homozygous ApoE4 genotype and confirmatory biopsy                         |
| Primary CNS Angetis                         | TO    | Peak around age 50, affects more men than women | Cognitive impairment and multifocal neurological symptoms                          | Multiple hyperintense lesions in gray or white matter on T2 | CNS angiogram, brain, and meningeal biopsy | High doses of intravenous corticosteroids, immunosuppression               |
| Cerebral venous sinus thrombosis            | ACE   | Adults affect more women than men, pregnancy, hypercoagulable states | Cognitive impairment, confusion, focal neurological signs, and headache            | Venous clot, hyperintense gray and white matter lesions on T2, possible restricted diffusion or hemorrhage | Normal                          | Venography magnetic resonance testing and hypercoagulability              |                                                                             |
| Infectious                                  |       |                            |                                                                                   |                              |                                |                                  |                                                                             |
| Neurosyphilis                               | S     | Consider risk factors      | Cognitive impairment, depression, psychosis, and pupillary abnormalities             | It May be normal or have nonspecific atrophy                                      | Serum RPR                        | Crystal penicillin G intravenously for 10–14 days                         |
| Whipple's disease                           | S     | Adults, rare in older adults | Dementia, psychiatric symptoms, movement disorders, ophthalmoplegia, myoclonus, gastrointestinal complaints | Normal versus FLAIR hyperintensities in MTL, midbrain, and diencephalon         | PCR for the detection of Treponema whippiei | Jejunal biopsy                  | Ceftriaxone 2 g/d for 2 weeks – Cotrimoxazole for 1 year or more           |
| Lyme disease                                | S     | Any age, variable prevalence in different regions | Dementia, cranial neuropathy, meningitis, psychosis, polyradiculopathy; neurological manifestations are late | Normal in most cases | Lymphocytic pleocytosis, intrathecal production of Abs | Serology                        | Ceftriaxone 2 g/d for 14 days                                                |
| HIV dementia                                | ACE   | Seroconversion, HIV (+) older adults, CD4 count decreased | Psychomotor slowdown, executive dysfunction, depression, movement disorders         | Cortical atrophy, nonspecific changes in the white matter                          | Increased protein, mild pleocytosis | HIV serology, serum viral load, and dCSF                                | HAART that penetrates CNS                                                   |

Table 1. The most common causes or potentially treatable causes of Dementia
| Disease                                | Start | Demographic characteristics | Clinical features                                           | NMR                                                                 | CSF                                                                 | Other tests                                                                 | Treatment                                                                 |
|----------------------------------------|-------|-----------------------------|-------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Herpetic meningoencephalitis           | TO    | Any age                     | Altered level of consciousness, focal deficits, seizures, behavioral changes, fever | Hyperintensity in the medial temporal lobe in FLAIR, asymmetric necrosis, posterior hemorrhagic | Pleocytosis at the expense of lymphocytes, ↑ RBC, HSV-1 CRP + | EEG: focal abnormalities, PLEDS                                          | Acyclovir IV for 14–21 days (start earlier if suspected)                   |
| Toxic–metabolic                        |       |                             |                                                             |                                                                      |                                                                      |                                                                            |                                                                            |
| Wernicke syndrome                      | TO    | Risk factors: akoholism, malnutrition | Cognitive disability, eye movement abnormalities, ataxia | T2 hyperintensity in the medial thalamus and mammillary bodies       | No diagnosis                                                        | –                                                                           | Thiamine                                                                  |
| Myelolysis extrapontine                | TO    | The rapid correction in electrolyte disturbance (e.g. hyponatremia) | Symptoms develop after a few days, encephalopathy, movement disorders, para/quadriaparesis | Hyperintensity in T2 with contrast at the level of the bridge, cerebellum, basal ganglia, and thalami that may appear after several days | No diagnosis                                                        | –                                                                           | Symptomatic                                                                |
| Vitamin B12 deficiency                 | S     | Older adults, pernicious anemia, veganism, fad diets | Cognitive disability (rare but manageable), sensory ataxia, paresthesias | Non-diagnostic                                                        | No diagnosis                                                        | ↓ Vitamin B12, ↑ Homocysteine                                              | B12 vitamin                                                                |
| Acquired hepatocerebral degeneration    | S     | Cirrhosis (portosystemic shunt) | Apathy, inattention, parkinsonism, cranial dysequilibrium | Pale hyperintensity in T1, standard T2                              | No diagnosis                                                        | –                                                                           | Treatment of liver disease, if irreversible, liver transplantation is used |
| Acute intermittent porphyria           | ACE   | 20–30. F > M                | Abdominal pain, autonomic dysfunction, behavioral changes, altered state of consciousness | Normal                                                                 | No diagnosis                                                        | Elevated PBG/ALA in urine                                                 | Carbohydrates, intravenous heme arginate; avoiding certain medications and metabolic disorders |
| Autoimmune                              | ACE   | Median 19 years. F > M      | Flu-like prodrome, prominent psychiatric features (psychosis), hyperkinesia, autonomic instability | Average at 45%. Hyperintensity in T2 at the level of the cerebral and cerebellar cortex with meningeal contrast | Pleocytosis at the expense of lymphocytes, common OCB | Screening for tumor (especially ovarian teratoma)                          | (25% relapse. Treatment with Rituximab and cyclophosphamide) Immune-mediated therapy (Ig, steroids, plasmapheresis) |
| NMDAR encephalopathy                   | ACE   | Median 19 years. F > M      |                                                             |                                                                      |                                                                      |                                                                            |                                                                            |
| Encephalopathy with VGKC antibodies (LG11 antigen) | S     | Median 60 years             | Limbic encephalitis, hyponatremia, seizures, myoklonus, ataxia, unilateral branchial-facial spasms | Medial temporal lobe hyperintense in FLAIR at 85%; could be normal | Normal or elevated proteins, Uncommon OCB | <20% with tumors (SCLC, thymoma) EEG slowing down; with baseline rhythm slowing | Infrequent relapse Immune-mediated therapy (Ig, steroids, plasmapheresis) |
| Disease                                | Start | Demographic characteristics<sup>a</sup> | Clinical features                                                                 | NMR                           | CSF                        | Other tests                                                                 | Treatment                                                                 |
|----------------------------------------|-------|-------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------|---------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Limbic encephalitis (paraneoplastic)   | S     | Any age (depends antibody)                | Neuropsychiatric symptoms (anxiety, hallucinations), seizures, cognitive impairment, headache, tremor, subacute onset, fluctuating course | Hyper MTL in T2/FLAIR; can be normal | Lymphocytic pleocytosis, normal or elevated proteins, ±OCB | Most frequent AC: anti-CV2/CRMP5, Hu, Ma 2 (10% seronegative) EEG slowing down | Therapy immune-mediated (Ig, steroids, plasmapheresis) |
| Acute demyelinating encephalomyelitis  | TO    | More frequent in children                 | Post-flu-like prodrome vaccination/viral infection; encephalopathy with multifocal neurological signals | Multifocal T2/FLAIR hyper, sometimes with EC | Mild pleocytosis protein <100 mg/dL | –                                                                          | Intravenous corticosteroids (or plasmapheresis and immunoglobulin) |
| Metastatic/neoplastic                  |       |                                           |                                                                                   |                               |                           |                                                                            |                                                                            |
| Primary CNS lymphoma                   | S     | Most 50–70 years                          | Neuropsychiatric symptoms, deficits neurological focal, convulsions               | Focal hiccups or hyper T2 lesions with CE; rarely Hyper DWI | Lymphocytic pleocytosis, flow cytometry for lymphoma cells | High LDH, ESR; biopsy | Specific treatment for lymphoma |
| Glionoma cerebri                       | S     | Older adults                              | AMS, dementia, seizures, headache, focal deficits                                | T2/FLAIR hyper in 2+ lobes; ± mass effect; ±CE | –                          | Brain biopsy                                                              | Radiation±chemotherapy |
| Iatrogenic/innate errors of metabolism |       |                                           | Attention to the relationship of time between the start of drug use and cognitive symptoms | No diagnosis | No diagnosis | No diagnosis | Discontinuation |
| Neurodegenerative                      |       |                                           |                                                                                   |                               |                           |                                                                            |                                                                            |
| CJD                                    | S     | Mainly 50–70 years; M = F                 | Subacute cognitive impairment with behavioral symptoms, pyramidal, extrapyramidal, cerebellar, myoclonus, or visual | Hyper cortical or subcortical in DWI | ↑ Total Tau, ↑ 14-3-3 and ↑ NSE | EEG: deceleration; PWCs | Palliative and symptomatic management |
| Alzheimer disease                       | S     | >60 years                                  | Early short-term memory impairment                                               | Hippocampal atrophy, then extending to the temporal, parietal, and frontal region | ↓ Aβ 42 ↑ phospho-Tau, ↑ total Tau | PET with the amyloid ligand | Palliative approach care |
### Disease Demographic Characteristics Clinical Features NMR CSF Other Tests Treatment

| Disease | Start | Characteristics | Clinical Features | NMR | CSF | Other Tests | Treatment |
|---------|-------|-----------------|-------------------|-----|-----|-------------|-----------|
| LBD     | S     | >50 years       | Can be found cognitive dysfunction, parkinsonism symptoms, visual hallucinations, behavioral changes, fluctuations | Normal or nonspecific atrophy | No diagnosis | FDG-PET: occipital hypo | Palliative approach care |
| BvFTD   | S     | 40–70 years     | Behavioral changes (apathy, disinhibition, loss of empathy/sympathy, repetitive behaviors), executive dysfunction | Temporal or frontal atrophy | No diagnosis | FDG-PET: frontal/temporal hypo | Palliative approach care |
| CBS     | S     | 50–70 years     | Can be found cognitive dysfunction, asymmetric motor abnormalities, or aphasia | Asymmetric, parietal, or frontal atrophy is possible | In AD etiology, ↓ Aβ42 ↑ phospho-tau, ↑ total Tau | – | It depends on the etiology, AD versus primary tauopathy |

### Seizures/systemic

| Disease | Type | Characteristics | Clinical Features | NMR | CSF | Other Tests | Treatment |
|---------|------|-----------------|-------------------|-----|-----|-------------|-----------|
| Hypertensive encephalopathy | TO | Mainly in uncontrolled hypertension, eclampsia or chemotherapy | Headaches, confusion, visual changes, seizures, and coma are underlining symptoms | Hyper FLAIR in occipitoparietal WM | No diagnosis | – | Treatment of hypertension |
| Seizures/NCSE | TO | Older adults | Cognitive dysfunction, fluctuations in alertness | It's Hyper DWI in cortical or subcortical GM | You could have mild pleocytosis | EEG | AEDs |

This list is not intended to be exhaustive but focuses on the most common causes or potentially treatable causes. In addition, the most typical abnormalities observed in the complementary tests are listed, which may not be present in all cases.

A: acute (days/weeks); ACA, anterior cerebral artery; AChE, acetylcholinesterase inhibitors; AED, antiepileptic drug; A, acute (days/weeks); ACA, anterior cerebral artery; AChI, acetylcholinesterase inhibitors; AED, antiepileptic drug; ALA, delta aminolevulinic acid; AMS, altered mental status; bvFTD, behavioral variant of frontotemporal dementia; CAA, cerebral amyloid angiopathy; CBS, corticobasal syndrome; CE, contrast enhancement; CJD, Creutzfeldt-Jacob disease; ESR, erythrocyte sedimentation rate; GM, gray matter; Hyper, hyperintensities/hypermetabolism; Hypo, hypointensities/hypometabolism; LBD, Lewy body dementia; LDH, lactate dehydrogenase; MMA, methylmalonic acid; MRV, magnetic resonance venography; NCSE, non-convulsive status epilepticus; OED, oligoclonal bands; PBG, porphobilinogen; PCA, posterior cerebral arterial; PE, plasma exchange; RBC, red blood cells; S, subacute (weeks/months); SCLC, small cell lung carcinoma; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin/norepinephrine reuptake inhibitor; SNRI, serotonin/norepinephrine reuptake inhibitor; WM, White matter.

*aAges, sex, or most frequent risk factors.*

*bVGKC complex encephalopathy is due to inactivated antibodies to leucine-rich glioma 1 (LGI 1).*
Clinically, it is common to find subacute limbic encephalitis that evolves into an anamnestic deficit related to REM sleep disturbances and epileptic seizures [20]. It has also been associated with myoclonic movements (dystonic faciobrachial seizure or tonic seizure), RPD, CJD, hyponatremia. In 47% of cases, the brain MRI did not present alterations [22–24]. Interictal and ictal findings and focal slowing can be found on the electroencephalogram. There were findings of rapid and generalized attenuation in the case presented during and after episodes of faciobrachial seizure, moderate lymphocytosis, and increased protein concentration in the CSF study [25].

Given the clinical suspicion of encephalopathy associated with antibodies against the VGKC complex with CA's presence against LGI1 and Caspr2, the most frequently used first-line immunotherapies are steroids, intravenous immunoglobulins, and plasma exchange, individually or in combination. The combination of steroids with intravenous immunoglobulins can also be used. If there is no response to these immunotherapies, the following strategy includes rituximab and cyclophosphamide [26]. Also, 70–80% of patients respond adequately to previous treatment. However, some patients may persist with residual memory disorders [27].

Anti-NMDAR encephalitis is a serious but treatable disorder that frequently affects children and adolescents, yet it continues to be under-recognized. However, anti-NMDAR encephalopathy is recognizable from the point of view of its clinical features [28, 29].

Most patients with anti-NMDAR encephalitis develop a disease that goes through different stages and can start from psychosis, memory deficits, seizures, the disintegration of language and progression to a catatonic state, abnormal movements, autonomic and respiratory instability. In our case, a previously healthy 49-year-old woman had been experiencing working memory loss, disorientation, inappropriate behavior, structured visual hallucinations, and finally, myoclonic seizures, which progressively increased to epileptic encephalopathy [30, 31].

According to the literature, the disorder predominantly affects children and young adults. The female population around 18 years of age and the black race are the most affected. They usually develop ovarian teratoma and various psychiatric disorders such as amnesia, seizures, dyskinesias, autonomic dysfunction, and decreased level of consciousness [30, 32].

A study showed that antibodies against NMDAR heteromers containing NR2B and NR2A are associated with more severe encephalitis. Another study showed that patients treated with tumor resection and immunotherapy (corticosteroids, intravenous immunoglobulin, or plasma exchange) respond rapidly to treatment and less frequently require second-line immunotherapy than patients without a tumor with similar initial immunotherapy [30–33].

For the diagnosis of anti-NMDAR encephalitis, an immunological cause was confirmed in our case using a brain MRI showing an inflammatory process, described as hyperintense lesions on T2 in the right basal nucleus with diffusion restriction [14, 15, 30]. The literature shows that the diagnosis of anti-NMDAR encephalitis can be made by employing MRI (FLAIR), where it is expected; otherwise, anomalies that enhance the contrast in cortical (brain/cerebellum) or subcortical regions (hippocampus, basal ganglia, white matter, and stem) up to 33%. In contrast, PET shows a predominantly frontal cerebral hypermetabolism that correlates with the severity of the disease [30, 31].

On the other hand, the literature reveals that EEG is potentially more helpful, but epileptic activity is rare, and in the initial screening, almost 30% did not have EEG finding reported. Still, it is characterized by severe generalized slowing (delta range frequencies), triphasic wave, and focal abnormalities in 18.4%, most commonly in the temporal, frontotemporal, and frontal regions. The presence of EDB principally in NMDARE, EDB was not associated with the presence of orofacial dyskinesia or movement disorder, suggesting that EMG artifact is not responsible for this pattern. Epileptiform discharges as sharp waves or periodic lateralized epileptiform discharges and generalized periodic epileptiform discharges were seen in 15%.
In our case, EEG findings evidenced continuous attenuation and no good sleep patterns, as well as delta brush and triphasic wave, identical to the literature [32, 33].

Regarding the CSF analysis, lymphocytic pleocytosis or oligoclonal bands are evidenced. However, the basic CSF parameters may be expected first, as in our 2 patients where the CSF analysis showed typical results [34, 35].

There was an RPD associated with an epileptic condition challenging to manage or refractory to treatment. As no other differential diagnosis was found, anti-NMDAR antibodies were requested.

**Conclusion**

RPD continues to be a problematic pathology to diagnose. Therefore, we propose establishing a clear flow chart for non-neurologist professionals to make early recognition of the pathology and select candidates for immune-mediated therapy to reduce complications.

As reported in the literature, our cases presented a high pretest diagnostic probability, where we could conclude that the triad of altered behavior, alterations in movement, and seizures accompanied by cognitive changes or sleep patterns, imply complement with EEG, MRI, with which we could indicate a therapy in the event of nonconfirmation by immunological tests. Considering that there is no option of accessing antibody tests in all countries, using clinical scales as a prognostic factor has been proposed to reduce morbidity and mortality in these patients.

It is also convenient to carry out investigations that aim at the creation and validation of neuropsychological scales, aimed at identifying in a specific way this type of dementia, especially in population with low schooling; in the same way, the results of these scales would be directed to establish plans of functional neurorehabilitation, with the aim of slowing down the neurocognitive deterioration in these patients, and thus, in advancing to a more severe stage of their diagnosis of dementia.

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**Statement of Ethics**

The study has been carried out taking as a reference the ethical principles for the development of research or experimentation on human beings, in this case, the Declaration of Helsinki (revised in 2013), the Declaration of Bern, and resolution 008430 of October 4, 1993, of the Ministry of Social Protection of the Republic of Colombia for the ethical aspects of research on human beings. Ethical review and approval were obtained from the Ethical Committee of the Pacific’s Neurological Institute on April 5th, 2021 for the study on human participants following the local legislation and institutional requirements. The authors state
that the patients and their immediate caregivers gave their written approval to write and publish the article, including the following documents: their clinical history, the images, test results, and additional data found in this article. Written informed consent was obtained from the patient’s next of kin/guardian along with the patient’s sign. In addition, written informed consent had the address and contact number of the patient. In case 1, written informed consent was obtained from the patient and from the patient’s next of kin for publication of the details of their medical case and any accompanying images. In case 2, consent for publication of the details of their medical case and any accompanying images was obtained only by the patient. Finally, in case 3, written informed consent was obtained from the patient and from the patient’s next of kin for publication of the details of their medical case and any accompanying images.

**Conflict of Interest Statement**

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Author Contributions**

Carlos Andrés Clavijo, Ana María Portilla Buenaventura, Galo Santiago Benavides Albornoz, Juan José Muñoz Cabrera, María Camila Murillo Reyes, and Alejandra Chauvez Gallego designed the study, wrote the manuscript’s first draft, and interpreted the data. Carlos Alberto Hurtado González, Sebastian Ospina Otalvaro, Carlos Steven Marmolejo Escobar, Karen Julieth Quebrada Mera, Paola Andrea Gutierrez Lenis, Lina María Arango García, and Armando Lucumi contributed to the data analysis, the revision of the bibliography, a revised version of the manuscript, and the adaptation of the article to the journal. All authors and co-authors were involved in interpreting and analyzing findings. All proved the manuscript, contributed to the critical intellectual content, and wrote and approved the final manuscript.

**Data Availability Statement**

All data that support the findings of this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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