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Case Series – General Neurology

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

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Rapidly progressive dementia · Voltage-gated potassium channel complex · NMDAR · Encephalitis · Creutzfeldt-Jakob disease

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. ***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. ***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. ***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

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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 mm^3 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

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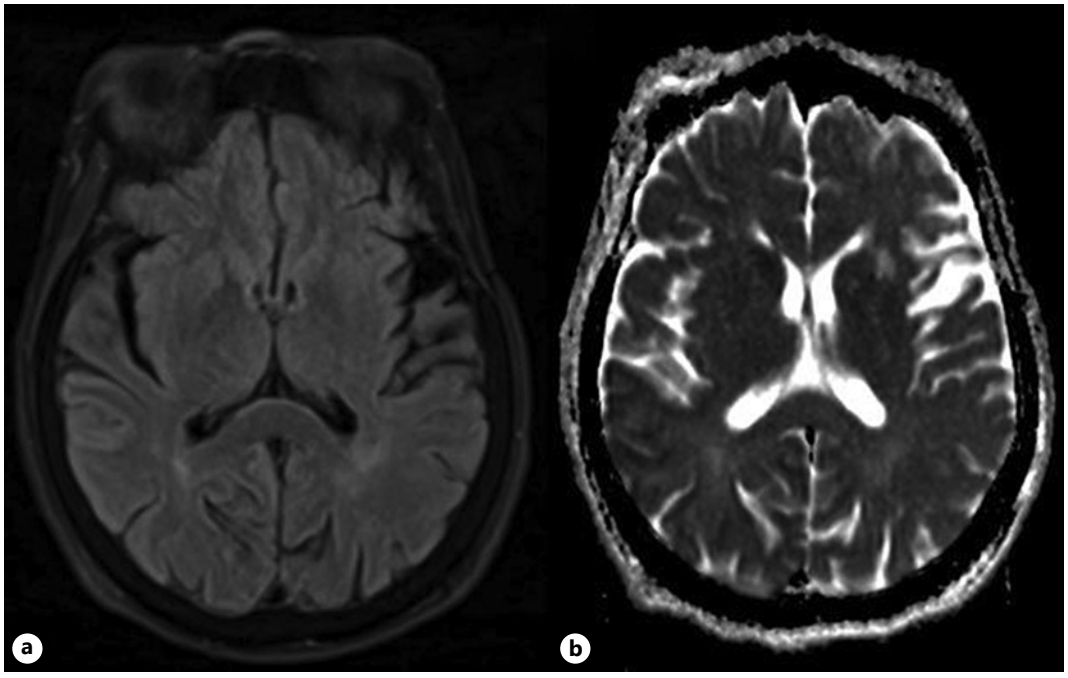

Fig. 1. Case 1: **a** Axial T2-weighted Fluid attenuated inversion recovery (FLAIR) image. It is showing slightly high signal intensity (red flag) in the caudate nucleus bilateral. **b** Axial MRI ADC (Apparent diffusion coefficient). Signal decrease in the bilateral caudate nucleus higher left.

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

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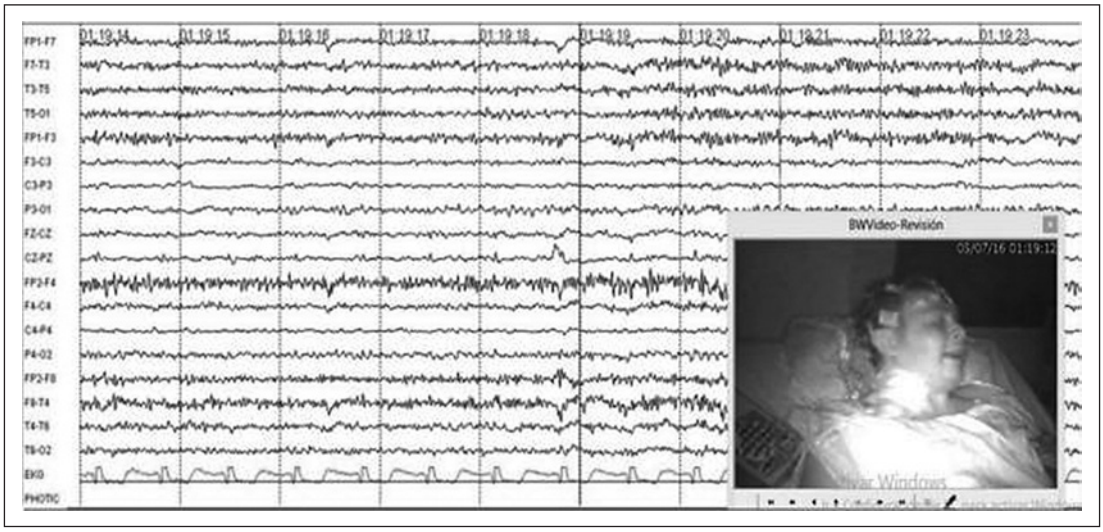

Fig. 2. Case 2: 12 h of EEG with LFF at 1 Hz and HFF at 70 Hz. It Illustrates continuous fast activity mixed with muscle artifact during and after faciobrachial dystonic seizure.

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

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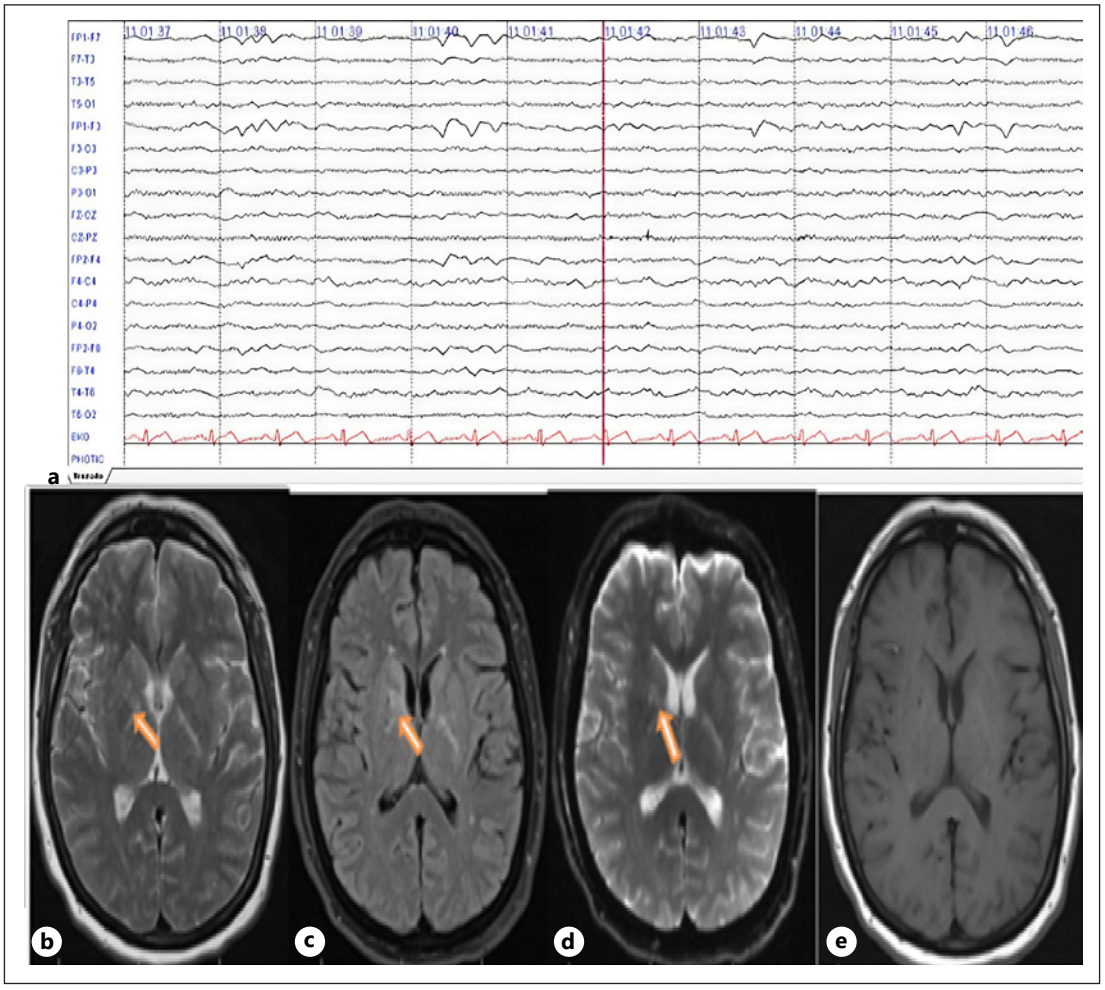

Fig. 3. CASE 3: **a** 12 h of EEG with LFF at 1 Hz and HFF at 70 Hz. Evidence bilateral frontal intermittent slowing complex. **b**–**e** Hyperintense lesions on T2 and Fluid attenuated inversion recovery (FLAIR) MRI image compromised the basal ganglia right side with restricted diffusion, no lesion enhancing.

1 (LGI1) 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].

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Table 1. The most common causes or potentially treatable causes of Dementia

Disease	Start	Demographic characteristics[a]	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)		Homozygous ApoE4 genotype and confirmatory biopsy	
Primary CNS Angeitis	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	Could show pleocytosis and elevated proteins	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	Anticoagulant
Infectious							
Neurosyphilis	S	Consider risk factors	Cognitive impairment, depression, psychosis, and pupillary abnormalities	It May be normal or have nonspecific atrophy	CSF and VDRL	Serum RPR	Crystalline 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 Tropheryma whipplei	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 CSF	HAART that penetrates CNS

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Table 1 (continued)

Disease	Start	Demographic characteristics[a]	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: alcoholism, malnutrition	Cognitive disability, eye movement abnormalities, ataxia	T2 hyperintensity in the medial thalamus and mammillary bodies	No diagnosis	–	Thiamine
Myelinolysis extrapontine	TO	The rapid correction in electrolyte disturbance (e.g., hyponatremia)	Symptoms develop after a few days, encephalopathy, movement disorders, para/quadriparesis	Hyperintensity in T2 with contrast at the level of the bridge, cerebellum, basal ganglia, and thalamus 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 ↑ AMM ↑ Homocysteine	B12 vitamin
Acquired hepatocerebral degeneration	S	Cirrhosis (portosystemic shunt)	Apathy, inattention, parkinsonism, cranial dyskinesia	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							
NMDAR encephalopathy	ACE	Median 19 years. F > M	Flu-like prodrome, prominent psychiatric features (psychosis), hyperkinesis, 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)
Encephalopathy with VGKC antibodies (LGI1 antigen)	S	Median 60 years	Limbic encephalitis, hyponatremia, seizures, myoclonus, ataxia, unilateral brachial-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 base rhythm slowing	Infrequent relapse Immune-mediated therapy (Ig, steroids, plasmapheresis)

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Table 1 (continued)

Disease	Start	Demographic characteristics[a]	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, plasmaféresi s)
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
Gliomatosis 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							
Medicament os	ACE	Older adults	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	↓ A β 42 ↑ phospho -Tau, ↑ total Tau	PET with the amyloid ligand	Palliative approach care

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Table 1 (continued)

Disease	Start	Demographic characteristics[a]	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, desinhibició n, 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	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							
Hypertensive encephalopathy	TO	Mainly in uncontrolled hypertension, eclampsia or chemotherapy	Headaches, confusion, visual changes, seizures, and coma are underlighting 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; AChl, 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, hyperintensities/hypometabolism; LBD, Lewy body dementia; LDH, lactate dehydrogenase; MMA, methylmalonic acid; MRV, magnetic resonance venography; NCSE, non-convulsive status epilepticus; OCB, 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; WM, White matter.

[a]Ages, sex, or most frequent risk factors.

[b]VGKC 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 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%.

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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 Maria Arango Garcia, 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.

References

1 Datri L, Quiroga J, Reisin R, Rojas G, Young P. Deterioro cognitivo rápidamente evolutivo. Análisis de 6 casos Rapidly progressive dementia; 2018 Mar.
2 Geschwind MD, Shu H, Haman A, Sejvar JJ, Miller BL. Rapidly progressive dementia. Ann Neurol. 2008;64(1):97–108.
3 Lancaster E, Dalmau J. Neuronal autoantigens-pathogenesis, associated disorders, and antibody testing; 2012.
4 Frost B, Diamond MI. Prion-like mechanisms in neurodegenerative diseases. Nat Rev Neurosci. 2010;11(3):155–9.

5 Ganor Y, Goldberg-Stern H, Amrom D, Lerman-Sagie T, Teichberg VI, Pelled D, et al. Autoimmune epilepsy: some epilepsy patients harbor autoantibodies to glutamate receptors and dsDNA on both sides of the blood-brain barrier, which may kill neurons and decrease in brain fluids after hemispherotomy. Clin Dev Immunol. 2004 Sep–Dec;11(3–4):241–52.
6 Brenner T, Sills GJ, Hart Y, Howell S, Waters P, Brodie MJ, et al. Prevalence of neurologic autoantibodies in cohorts of patients with new and established epilepsy. Epilepsia. 2013 Jun;54(6):1028–35.
7 Prado CAC, Gallego AC. Autoimmune epilepsy—a new goal of science: report two cases in the San Jose Hospital, Bogota, Colombia. J Neurol Stroke. 2019;9(3):129–32.
8 Kim MO, Geschwind MD. Clinical update of Jakob-Creutzfeldt disease. Curr Opin Neurol. 2015;28(3):302–10.
9 Munné Díaz C, Grau Solà M, Torreño Sánchez M. Enfermedad de Creutzfeldt-jacob. Rev Científica la Soc Española Enfermería Neurológica [Internet]. Medicina en español. 2013 Jan 1 [cited 2020 Aug 27];37(1):29–32.
10 Sanchez-Juan P, Green A, Ladogana A, Cuadrado-Corrales N, Sáanchez-Valle R, Mitrováa E, et al. CSF tests in the differential diagnosis of Creutzfeldt-Jakob disease. Neurology. 2006 Aug 22;67(4):637–43.
11 Collins SJ, Sanchez-Juan P, Masters CL, Klug GM, van Duijn C, Poleggi A, et al. Determinants of diagnostic investigation sensitivities across the clinical spectrum of sporadic Creutzfeldt-Jakob disease. Brain. 2006 Sep; 129(Pt 9):2278–87. Epub 2006 Jul 1.
12 Puoti G, Bizzi A, Forloni G, Safar JG, Tagliavini F, Gambetti P. Sporadic human prion diseases: molecular insights and diagnosis. Lancet Neurol. 2012;11(7):618–28.
13 Zerr I, Pocchiari M, Collins S, Brandel JP, de Pedro Cuesta J, Knight RS, et al. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. Neurology. 2000;55(6):811–5.
14 van Sonderen A, Thijs RD, Coenders EC, Jiskoot LC, Sanchez E, de Bruijn MA, et al. Anti-LGI1 encephalitis: clinical syndrome and long-term follow-up. Neurology. 2016 Oct 4;87(14):1449–56. Epub 2016 Sep 2.
15 Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol. 2011 May;69(5):892–900. Epub 2011 Mar 17.
16 Ekizoglu E, Tuzun E, Woodhall M, Lang B, Jacobson L, Icoz S, et al. Investigation of neuronal autoantibodies in two different focal epilepsy syndromes. Epilepsia. 2014;55(3):414–22.
17 Liimatainen S, Peltola J, Hietaharju A, Sabater L, Lang B. Lack of antibodies to NMDAR or VGKC-complex in GAD and cardiolipin antibody-positive refractory epilepsy. Epilepsy Res. 2014 Mar;108(3):592–6. Epub 2014 Jan 6.
18 Lai M, Huijbers MG, Lancaster E, Graus F, Bataller L, Balice-Gordon R, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. 2010;9:776–85.
19 Lancaster E, Huijbers MG, Bar V, Boronat A, Wong A, Martinez-Hernandez E, et al. Investigations of Caspr2, an autoantigen of encephalitis and neuromyotonia. Ann Neurol. 2011;69:303–11.
20 Klein CJ, Lennon VA, Aston PA, McKeonO'Toole O, O'Toole A, Quek A, et al. Insights from LGI1 and CASPR2 potassium channel complex autoantibody subtyping. JAMA Neurol. 2013;70:229–34.
21 Irani R, Alexander R, Waters P, Kleopa KA, Pettingill P, Zuliani L, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain. 2010;133:2734–48.
22 Montojo MT, Petit-Pedrol M, Graus F, Dalmau J. Clinical spectrum and diagnostic value of antibodies against the potassium channel related protein complex. Neurologia. 2015;30(5):295–301.
23 Fukata Y, Lovero KL, Iwanaga T, Watanabe A, Yokoi N, Tabuchi K, et al. Disruption of LGI1-linked synaptic complex causes abnormal synaptic transmission and epilepsy. Proc Natl Acad Sci U S A. 2010;107:3799–804.
24 Yu YE, Wen L, Silva J, Li Z, Head K, Sossey-Alaoui K, et al. Lgi1 null mutant mice exhibit myoclonic seizures and CA1 neuronal hyperexcitability. Hum Mol Genet. 2010;19:1702–11.
25 Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12:157–65.
26 Iwasaki Y, Tatsumi S, Mimuro M, Kitamoto T, Hashizume Y, Yoshida M. Relation between clinical findings and progression of cerebral cortical pathology in MM1-type sporadic Creutzfeldt-Jakob disease: proposed staging of cerebral cortical pathology. J Neurol Sci. 2014 Jun 15;341(1–2):97–104.
27 Iwasaki Y. Creutzfeldt-Jakob disease [Internet]. Neuropathology. 2017 Apr 1 [cited 2020 Nov 8];37(2):174–88. http://doi.wiley.com/10.1111/neup.12355.
28 Otto M, Wiltfang J, Tumani H, Zerr I, Lantsch M, Kornhuber J, et al. Elevated levels of tau-protein in cerebrospinal fluid of patients with Creutzfeldt-Jakob disease [Internet]. Neurosci Lett. 1997 Apr 11 [cited 2020 Nov 8];225(3):210–2.
29 Muayqil T, Gronseth G, Camicioli R. Evidence-based guideline: diagnostic accuracy of CSF 14-3-3 protein in sporadic creutzfeldt-jakob disease: report of the guideline development subcommittee of the American academy of neurology [Internet]. Neurology. 2012 Oct 2 [cited 2020 Nov 8];79(14):1499–506.
30 Geschwind MD, Potter CA, Sattavat M, Garcia PA, Rosen HJ, Miller BL, et al. Correlating DWI MRI with pathological and other features of Jakob-Creutzfeldt disease. Alzheimer Dis Assoc Disord. 2009 Jan–Mar;23(1):82–7.
31 Will RG, Ironside JW. Sporadic and infectious human prion diseases. Cold Spring Harb Perspect Med. 2017 Jan 3 [cited 2020 Nov 8];7(1):a024364.
32 Moreno-Madrigal LG, Ernesto-Díaz A, Oikawa-Sakaguchi VM. Encefalitis paraneoplásica. Acta Méd Grupo Ángeles [Revista en La Internet]. 2017;15(2):139–42.
33 Gillinder L, Warren N, Hartel G, Dionisio S, O'Gorman C. EEG findings in NMDA encephalitis: a systematic review. Seizure. 2019;65:20–4.

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DOI: 10.1159/000525701

34 Reyes Botero G, Uribe Uribe CS, Hernández Ortiz OE, Ciro J, Guerra A, Dalmau Obrador J. Encefalitis paraneoplásica por anticuerpos contra el receptor de NMDA. Remisión completa después de la resección de un teratoma ovárico. RevNeurol. 2011;52(09):536–40.
35 Guanyabens-Buscà N, Casado-Ruiz V, Giné-Serven E, Palomeras E, Muriana D, Boix-Quintana E, et al. Encefalitis antirreceptor de NMDA. Diagnóstico y tratamiento precoz en pacientes con sintomatología psicótica aguda-subaguda. Rev Neurol. 2019;68(01):18–22.