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Progressive encephalopathy in a patient with diabetes mellitus: A case report and review of JCV-related neurological manifestations

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ABSTRACT

We present a case of a 66-year-old female patient with partially compromised immunity due to diabetes mellitus, exhibiting progressive encephalopathy characterized by balance issues, cognitive decline, and hallucinations. Magnetic resonance imaging (MRI) revealed widespread cerebral and cerebellar atrophy, and John Cunningham virus (JCV) – DNA was detected in the cerebrospinal fluid. This case highlights JCV encephalopathy as a potential diagnosis even in patients with partially weakened immune systems, expanding the recognized spectrum of JCV-associated neurological conditions beyond progressive multifocal leukoencephalopathy.

Keywords: JCV encephalopathy, Progressive encephalopathy, Cerebral atrophy

1. INTRODUCTION

John Cunningham virus (JCV), a human polyomavirus, is the etiologic agent of various neurological conditions, primarily affecting immunocompromised individuals. The virus is most often associated with progressive multifocal leukoencephalopathy (PML), a demyelinating disorder affecting oligodendrocytes and resulting in significant neurological impairment. However, JCV has also been linked to other conditions, including granule cell neuronopathy, JCV encephalopathy, and, more rarely, JCV meningitis. These less common manifestations of JCV infection often involve neuronal cells, with the virus infecting gray matter structures like cortical pyramidal neurons, leading to symptoms such as cognitive decline, behavioral changes, and motor impairment [1-3].

In this report, we present a case with JCV encephalopathy. This case highlights an unusual presentation of JCV-related neurological disease in an immunocompetent patient and underscores the broadening spectrum of JCV neurotropism and associated pathologies.

2. CASE REPORT

A 66-year-old female patient presented to our neurology outpatient clinic with progressive neurological symptoms. She had a 25-year history of diabetes mellitus (DM) and had been bilaterally blind for 10 years due to diabetic retinopathy. Four years prior, she had undergone metabolic surgery to manage her diabetes, with recent routine blood tests showing a blood glucose level of 124 mg/dL and an HbA1c of 5.0%.

Approximately five months before presentation, the patient began experiencing balance issues and frequent falls, which resulted in a lumbar vertebral fracture. Due to these issues, she was unable to walk for the past 1-2 months. Initially, her consciousness was normal, however, over the past two to three months, she started confusing rooms within her home, with intermittent, temporary improvements that did not resolve her symptoms entirely. Over the last month, her condition worsened, with the onset of visual hallucinations and beliefs in events or things that were not present. Her behavior became increasingly inappropriate in response to questions, and she struggled to perform daily activities. Notably, these symptoms fluctuated throughout the day, with episodes of worsening that progressively increased in frequency and severity.

The patient had bilateral total vision loss. On neurological examination, the patient was conscious and oriented to simple questions. Direct and indirect light reflexes were absent. Muscle strength in the lower extremities was 4/5. She had no sitting balance and was unable to stand.

The patient was administered the Mini-Mental State Examination (MMSE) and scored 9 points (Orientation: 6, Registration: 3, Attention and Calculation: 0, Recall: 0, Language: 0).

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The brain magnetic resonance imaging (MRI) revealed findings consistent with widespread cerebral and cerebellar atrophy, indicated by noticeable expansion in these regions (Figure 1). Electroencephalography (EEG) trace demonstrated theta slow waves, along with slow background activity indicating mild generalized cerebral dysfunction (Figure 2). Thoracic and lumbar spine MRIs revealed a compression fracture at the T5 level and broad-based disc protrusions at the L4-5 levels, compressing the bilateral nerve roots. A lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis included routine tests, cytology, and panels for antibodies to glutamic acid decarboxylase (anti-GAD), paraneoplastic, and autoimmune encephalitis markers. CSF biochemistry results were normal, and microscopy revealed no cells. The meningitis panel and panels for anti-GAD, paraneoplastic, and autoimmune encephalitis markers were negative. However, JCV PCR revealed detectable viral DNA at 500 copies. Consultation with the infectious diseases clinic confirmed negative findings for human immunodeficiency virus (HIV), Venereal Disease Research Laboratory (VDRL), and treponema pallidum hemaggulitation (TPHA) tests, with no history of antiretroviral or immunosuppressive drug use. The infectious diseases team recommended symptomatic management and follow-up.

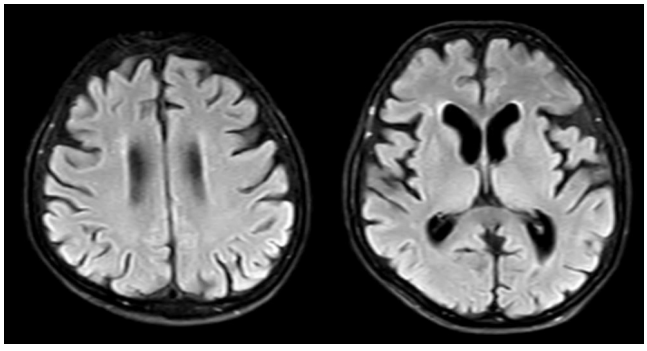

Figure 1. *The brain fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) showing widespread cerebral and cerebellar atrophy*

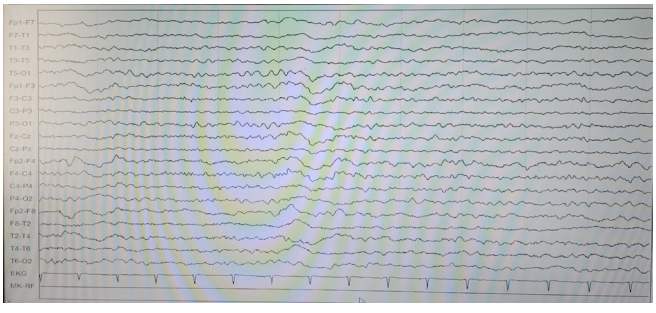

Figure 2. *Electroencephalography (EEG) trace demonstrating theta slow waves, along with slow background activity indicating mild generalized cerebral dysfunction*

3. DISCUSSION

John Cunningham virus is well-documented in causing PML and is related to white matter disorders, primarily affecting immunosuppressed patients. However, increasing evidence suggests that the virus can also infect neuronal cells, resulting in conditions like JCV encephalopathy. This unique presentation, wherein JCV infects cortical pyramidal neurons, has been observed in immunocompetent individuals and in those with mild immunosuppression. The present case aligns with descriptions of JCV encephalopathy, characterized by the virus's infiltration of cortical regions, manifesting as cognitive and motor deficits [3,4].

Key studies highlight that JCV encephalopathy may be linked to specific viral genetic variations, such as deletions in the agnoprotein gene, which can alter viral tropism toward neurons [1,2]. Furthermore, certain cases have demonstrated a predilection for the gray matter, indicating that JCV can infect multiple CNS cell types, including astrocytes and meningeal cells, expanding the virus's neurotropic potential beyond its classical white matter involvement seen in PML [5].

The patient's progressive symptoms over four months suggest a persistent infection with gradual neurological deterioration, mirroring other reports of JCV encephalopathy where symptoms evolve despite supportive care [4]. This aligns with findings in JCV meningitis and JCV encephalopathy cases, where hydrocephalus, cognitive decline, and altered mental status were noted despite therapeutic interventions like ventricular shunting and corticosteroids [2]. Given these insights, this case underscores the need for further studies on JCV's neurotropic behavior, particularly in non-immunocompromised hosts.

The presented case aligns with the emerging understanding that JCV can infect neuronal structures beyond the white matter typically affected in PML. JCV encephalopathy has been identified in immunocompromised patients and occasionally in immunocompetent hosts, resulting in significant cortical involvement and symptoms such as confusion, cognitive impairment, and altered mental status [2,4]. In this patient, the gradual onset of balance problems, followed by cognitive decline, disorientation, and hallucinations, mirror the progressive nature observed in other JCV encephalopathy cases. Notably, the patient's CSF analysis confirmed the presence of JCV DNA, an essential finding that supports JCV encephalopathy despite her immunocompetent status.

John Cunningham virus encephalopathy cases are frequently associated with specific viral genetic variants that may enhance JCV's ability to infect neurons, such as deletions in the Agnoprotein gene or variations in the viral regulatory regions [1,5]. These variants potentially alter the virus's neurotropism, allowing it to infect cortical and cerebellar neurons, as seen in this patient. The MRI findings of widespread cerebral and cerebellar atrophy further support the hypothesis of gray matter involvement, distinguishing this case from typical PML presentations that primarily affect the white matter [4].

The lack of paraneoplastic, autoimmune, or other infectious causes on CSF analysis, along with negative HIV, VDRL,

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and TPHA tests, add strength to the JCV encephalopathy diagnosis. This case highlights the importance of JCV in differential diagnoses for progressive encephalopathy, even in immunocompetent patients, and suggests that JCV's clinical spectrum may be broader than previously understood. Symptomatic management, as recommended for this patient, remains the primary approach in JCV encephalopathy due to limited antiviral options [3,5].

Conclusion

This case contributes to the growing body of literature on JCV encephalopathy, especially in cases where classic PML is absent. It highlights the virus's ability to infect and damage neuronal structures in gray matter, reinforcing the necessity for awareness of JCV's broader neuropathological spectrum. The findings support ongoing research on viral genomic mutations, which may influence JCV tropism and its associated clinical presentations. Clinicians should consider JCV encephalopathy in differential diagnoses of progressive encephalopathy, particularly in older patients presenting with cognitive decline and neurological deficits, even in the absence of marked immunosuppression.

Compliance with Ethical Standards

Ethical standards: This work was conducted ethically in accordance with the World Medical Association's Declaration of Helsinki.

Patient consent: The patient gave her consent for clinical information and images relating to her case to be reported in a medical publication.

Conflict of interest: The authors declare that they have no conflict of interest.

Authors' contributions: SO: Design, SO, AY: Supervision, MV, EA and BO: Resources and materials, MV, EA and BO: Data collection and/or processing, MV, EA and BO: Analysis and/or interpretation, SO: Literature search, SO: Writing the manuscript, SO: Critical review. All authors approved the final manuscript to be submitted.

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