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CASE REPORT
IN NEUROLOGY

A fulminant case of JC virus encephalopathy supporting a novel syndrome associated with JC virus infection of cortical neurons

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Abstract

The JC virus (JCV) is well known for causing progressive multifocal leukoencephalopathy (PML), a potentially fatal, demyelinating disease of the central nervous system (CNS). PML almost exclusively affects immunosuppressed patients, whereas it is rare in immunocompetent subjects. Recently, a new clinical entity, named JCV encephalopathy (JCVE), has been observed. We present the case of a 62-year-old male, with no identifiable immunosuppression, who developed aphasia and progressive reduction in consciousness. He had a six months insidious history of psychiatric symptoms. He passed away 3 weeks after onset of symptoms. On admission, brain MRI demonstrated a prominent grey matter involvement. Serological tests and cerebrospinal fluid analysis were all negative for infectious diseases. A whole-body CT scan was negative for cancer. Several EEGs showed a diffuse anterior theta activity with bilateral parietal epileptic periodic discharges. A second MRI imaging showed a more prominent non-enhancing grey and white matter involvement, compatible with PML. Finally, CSF- PCR for JCV was performed and resulted positive. To the best of our knowledge, our report is the second case of JCVE described so far. Similarly to our patient, the previous case developed symptoms consistent with a CNS disease with progressive clinical course. MRI abnormalities were initially restricted to the hemispheric grey matter and only later extended to the subcortical regions. Our case suggests that JCV infection should be considered even in immunocompetent patients presenting with unexplained cortical lesions and rapidly progressive encephalopathy.

KEY WORDS: leukoencephalopathies; JC virus; leukoencephalopathy, progressive multifocal.

Riassunto

Il JC Virus è una causa riconosciuta di leucoencefalopatia multifocale progressiva (PML), una malattia demielinizzante del sistema nervoso centrale (SNC) ad esito potenzialmente fatale. La PML colpisce soprattutto pazienti immunocompromessi, mentre è rara in soggetti immunocompetenti. Di recente è stata descritta una nuova entità clinica, denominata encefalopatia JCV (JCVE). Presentiamo il caso di un soggetto maschio di 62 anni, senza alcuna forma riconoscibile di immunosoppressione, giunto alla nostra osservazione con afasia e progressiva riduzione del livello di coscienza. Il paziente manifestava da sei mesi la subdola comparsa di sintomi di natura psichiatrica. E' deceduto dopo 3 settimane dall'insorgenza dei sintomi. Al ricovero, una RMN dell'encefalo evidenziava un importante interessamento della sostanza grigia. I test sierologici e l'analisi del liquido cerebrospinale erano tutti negativi per malattie infettive. Una TC total body era negativa per cancro. Diversi EEG mostravano un attività teta anteriore diffusa con scariche epilettiche periodiche parietali bilaterali. Una successiva RMN evidenziava un maggiore coinvolgimento della sostanza grigia e bianca, compatibile con PML. Infine, veniva effettuata la PCR per JCV che risultava positiva. Per quel che risulta agli autori del presente lavoro, questo è il secondo caso di JCVE descritto in letteratura. In modo analogo al nostro, nel primo caso descritto in letteratura il paziente aveva sviluppato dei sintomi compatibili con una malattia del sistema nervoso centrale ed un quadro clinico in progressivo peggioramento. Le alterazioni alla RMN erano inizialmente limitate alla sostanza grigia e solo in un secondo tempo si erano estese alle regioni subcorticali. Il nostro caso suggerisce che l'infezione JCV dovrebbe essere considerata anche in pazienti immunocompetenti che si presentano con lesioni corticali non giustificate da altre cause e con una encefalopatia rapidamente progressiva.

TAKE-HOME MESSAGE

The JC virus (JCV) is well known for causing progressive multifocal leukoencephalopathy (PML), a potentially fatal, demyelinating disease of the central nervous system (CNS). Our report is the second case of JCVE described in literature. The JCV infection should be considered even in immunocompetent patients presenting with unexplained cortical lesions and rapidly progressive encephalopathy.

Competing interests - none declared.

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INTRODUCTION

John Cunningham virus (JCV) is a human polyomavirus firstly identified in 1958 [1]. The virus is very common in general population and JCV antibodies can be found in a large percentage of healthy adults without causing any disease [2]. Asymptomatic primary JCV infection occurs in childhood and the virus remains latent in kidneys, lymphoid organs and in the brain [3, 4]. In patients with a profound cellular immunosuppression, including those with acquired immunodeficiency syndrome [5], hereditary immune dysfunction [6], haematological malignancies [7], transplant recipients [8] and patients treated with various immunosuppressive and immunomodulatory drugs for autoimmune disorders [9–11], JCV can reactivate and induce a lytic infection of oligodendrocytes, leading to a fatal demyelinating disease of the brain, known as progressive multifocal leukoencephalopathy (PML). PML can even occur in diseases conditioning a transient immune dysfunction, such as hepatic cirrhosis, malnutrition, kidney failure, dermatomyositis and pregnancy [12], whereas it is rare in immunocompetent patients [13, 14].

Although clinical presentation is strictly related to the location of white matter lesions, a classic clinical presentation of PML consists of a subacute neurologic syndrome that includes altered mental status, motor paresis, gait disturbances, and visual symptoms such as diplopia [3, 15]. Cortical symptoms, such as aphasia and epilepsy, have been often described in PML patients and they have been attributed more to white matter lesions that undercut relevant cortical areas than to grey matter involvement [15].

Recently, a single report of a new clinical entity, named JCV encephalopathy (JCVE), has been described [16]. In particular, JCVE mainly affects grey matter, conditioning an encephalitis–like clinical picture [16]. We report a second case of JCVE.

CASE REPORT

We present the case of a 62-year-old male who had a six months history of visual hallucinations and odd-behaviour with personality change, persecutory delusion and anxiety. Past medical history was positive for recurrent prostatitis and a surgically-removed thymoma.

Clinically, on admission, he showed aphasia and a progressive reduction in consciousness. Immediately after admission, a magnetic resonance imaging (MRI) of the brain was performed, showing a prominent non-enhancing signal abnormality (T2 and FLAIR sequences) bilaterally involving the temporal and fronto-basal lobes, together with the hippocampus bilaterally. Water diffusion restriction imaging showed signal abnormality involving bilaterally the temporal-parietal-occipital grey matter (Fig. 1). A lumbar puncture was performed and cerebrospinal fluid (CSF) analysis revealed a normal cell count and normal protein and glucose levels. PCR for neurotropic viruses (herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus), Chlamydia and Borrelia were negative.

On day 2, clinical condition deteriorated. Neurological examination showed a comatose patient, with miotic pupils. Photomotor reflex was absent. The doll's eye movements were absent. Corneal reflex was absent on the right. No spontaneous limb movement were detected. Tendon reflexes were symmetrically exaggerated. Plantar response was absent. Laboratory tests showed a slightly increased white blood cell and neutrophil counts. No kidney, liver or thyroid abnormalities were observed. Cancer marker tests were normal. Serological tests for HIV, Borrelia and syphilis were all negative. A brain computed tomography (CT) and a CT angiography were negative for a cerebral venous thrombosis. An electroencephalogram (EEG) showed temporal epileptic periodic discharges (Fig. 1) and an epileptic seizure was recorded. Thus, phenytoin was introduced with positive effects on consciousness and motor signs.

On day 5, a whole-body CT scan revealed a prostatic hypertrophy. No signs of malignancies were observed. Paraneoplastic antibodies on serum were negative.

On day 7, he developed bilateral palpebral

and right arm myoclonic jerks, and he became progressively unresponsive to painful and verbal stimuli. Myoclonic jerks were unresponsive to anti-epileptic treatment. Several electroencephalograms (day 7, 9, 14) were performed, showing a diffuse anterior theta activity with bilateral biphasic and triphasic epileptic periodic discharges, consisting with a grey matter involvement. Prion disease was then suspected and CSF was analysed looking for tau, phosphorylated tau, and 14.3.3 proteins.

On day 17, we performed a second MRI scan: it showed a more prominent grey and white matter involvement, without contrast enhancement, mass effect and aedema (Fig. 2). At this point, CSF- PCR for JCV was performed and resulted positive.

He passed out on day 20. Although CSF analysis showed high level of tau, phosphorylated tau and 14.3.3 proteins, post-mortem findings excluded prion disease in the brain. No malignancies were identified, whereas it confirmed the diagnosis of JCV infection in the brain.

DISCUSSION

Our patient presented with a subacute onset of psychiatric symptoms, cognitive decline and aphasia. Because initial clinical, radiological and neurophysiological findings were consistent with a rapidly progressive dementia accompanied by language and motor symptoms, prion disease was initially suspected. 14.3.3 protein, together with tau and phosphorylated tau, has been widely used as CSF biomarker in prion disease [17, 18], even though high level of 14.3.3 has been observed in other rapidly progressive dementia, probably as a consequence of the rapid neuronal damage [17, 19]. For this reason, its diagnostic value has been recently debated [18] and new diagnostic biomarkers have been described [20]. However, the gold standard for definitive diagnosis of prion disease is its histopathological confirmation [18] and post-mortem findings were negative for prion disease.

Because differential diagnosis in rapidly progressive dementia includes treatable and curable conditions [19], we ruled out the presence of other possible subacute encephalopathies, such as Hashimoto encephalopathy, autoimmune/paraneoplastic syndrome and HIV-related encephalopathy. Initial clinical and radiological presentation was not typical for PML and, as the patient did not have any actual underlying cause for immunosuppression and had not undergone immunosuppressive therapy, he was not initially tested for JCV.

The presence of an encephalopathy with a positive CSF-PCR for JCV is highly suggestive for a possible JCV grey matter infection. Such an unusual presentation, together with a negative medical history for immunosuppression, defines this unique case of JCVE.

In PML, demyelinating lesions are mainly located in the central nervous system white matter, whereas optic nerve and spinal cord are usually spared [21]. Since its first description in 1971 [22], neuropathological studies have described JCV-infected oligodendrocytes and reactive gliosis with enlarged astrocytes [21, 23]. More recently, infection of neurons and meningeal cells has been observed [15]. In particular, Du Pasquier et al. [24] demonstrated a productive JCV infection of cerebellar granule cell neurons in an HIV-positive patient. Then, Koralnik et al. [25] observed a JCV granule cell neuronopathy (JCV GCN) caused by a JCV variant with a specific tropism for cerebellar granule cell neurons. More recently, a fatal case of JCV meningitis in a HIV negative patient has been described [26]. Finally, Wuthrich et al. [16] reported a grey matter disease, with JCV primary infecting cortical pyramidal neurons. Thus, three new novel syndromes have been associated with JCV infection, in addition to classic PML: JCV granule cell neuronopathy, JCV meningitis, and JCV encephalopathy.

Similarly to JCV responsible for JCV GCN [27], JCV leading JCVE seems to be genetically different from the classic JCV-PML virus [28]. In particular, Dang et al. [28] identified a deletion in the agnoprotein gene and postulated that this particular mutation could allow for the virus to infected cortical grey

matter, with a high tropism for cortical pyramidal neurons [28]. In addition, because viral proteins have been observed in nuclei, cytoplasm and axons, JCVE virus has been thought to spread in the brain migrating through axons of infected neurons [16].

How genetic mutations in JCV DNA affect the identification of the virus by the immune system is unknown. To the best of our knowledge, the occurrence of PML in patients without known immunosuppression is very rare [13]. The concept that a transient immunosuppression can lead to a reactivation of the virus can explain some of the PML cases previously reported in patients with no underlying immunosuppressive disease [12]. In other cases, an idiopathic CD4+ lymphocytopenia can sometimes be observed in PML patients [6]. In our patient, despite a history of recurrent prostatitis, there were no medical reasons to suspect a dysfunction of the immune system. Although a T-cell subset count was not performed routine lymphocyte counts were constantly found to be normal. Because idiopathic CD4+ lymphocytopenia usually manifests with absolute lymphocytopenia [6], it's unlikely that our patient was affected by this condition.

JCVE is relatively new and very rare condition, with only one case described so far. Similarly to our patient, the previous case developed symptoms consistent with and encephalopathy and MRI abnormalities were initially restricted to the hemispheric grey matter and only later extended to the subcortical regions [9]. These data suggest that JCV should be also considered in evaluating patients presenting with unexplained cortical lesions and encephalopathy, regardless of the immune system status.

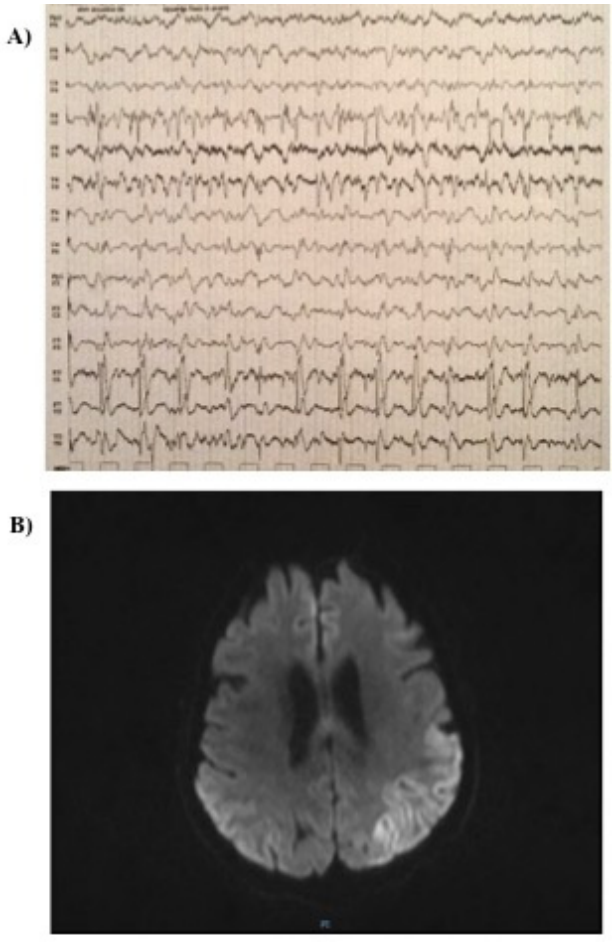

Figure 1. EEG and Brain MRI on admission. In A), EEG showing prominent bilateral parietal epileptic discharges. In B) DWI signal abnormalities bilaterallyinvolving the parietal cortex.

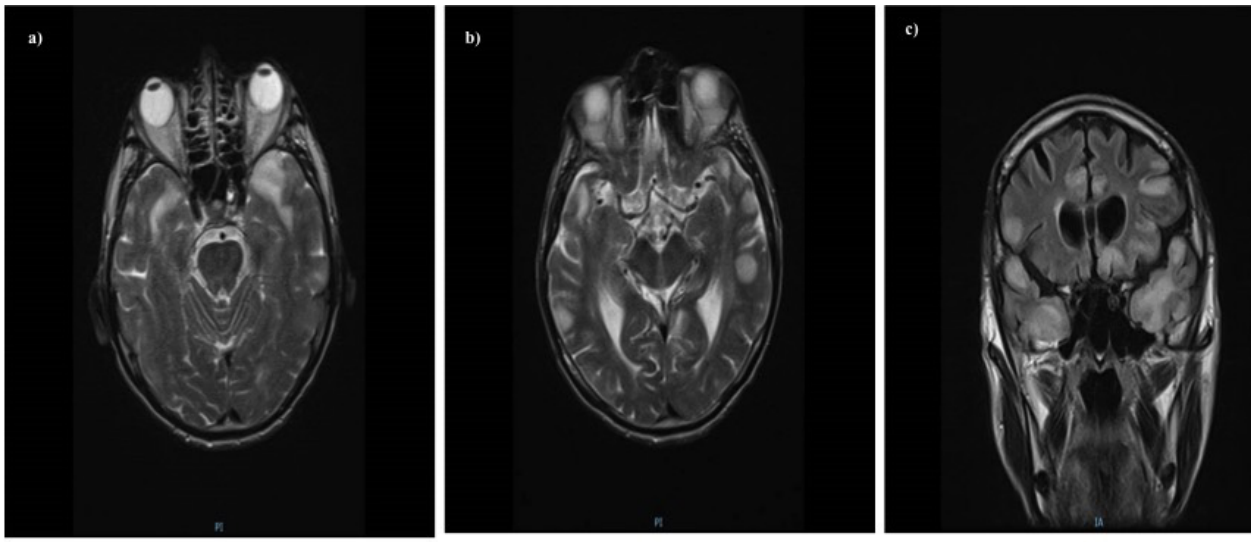

Figure 2. Progression in brain MRI abnormalities. T2 (a,b) and FLAIR (c) MRI imaging showed a more prominent non enhancing gray and white matter involvement.

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