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John Cunningham virus as cause of progressive multifocal leukoencephalopathy

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To the Editors

The JC virus was first isolated in 1971 and named the John Cunningham polyomavirus (JCV) after the patient from whose brain this virus was isolated [1]. This polyomavirus infects about 60% of the adult population worldwide, and is an opportunistic pathogen.

In the initial infection, the virus undergoes gene rearrangement and replicates in infected cells, transforming into a neurotropic form. JC virus primarily damages the brains of patients with innate immunodeficiency or those taking immunomodulatory medications. It has also been reported in association with rheumatological diseases, lymphoreticular malignancies, and post-organ transplantation immunosuppression. JC virus has a tropism for oligodendrocytes but has also been observed in astrocytes, granule neurons of the cerebellum, and cortical pyramidal neurons [2, 3].

This polyomavirus is aetiologically linked with progressive multifocal leukoencephalopathy (PML). Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system with a multifocal process.

The classic clinical presentation of PML includes subacute-to-chronic focal neurological deficits, depending on the location of the lesions. Initially, the diagnosis of PML was based on neuropathological examination characterised by a classic triad: demyelination, bizarre astrocytes, and oligodendroglial nuclear inclusions. The enlarged nuclei are often described in the literature as 'ground-glass' [4]. In clinical diagnostics, standard MRI pulse sequences are used for screening and monitoring PML. The typical magnetic resonance imaging (MRI) findings of PML are white matter lesions in different brain areas. They are usually hyperintense in T2-weighted and FLAIR sequences, reflecting white matter involvement [2]. Cerebrospinal fluid (CSF) examination is very helpful in excluding other diagnoses. The demonstration of JC virus by PCR in CSF is also considered diagnostic [4]. The use of a diagnostic algorithm in diagnosing fatal PML may expedite the correct diagnosis, but does not exhaustively identify the brain changes caused by the JC virus.

A 70-year-old woman presented to the clinic with left-sided hemiparesis (symptoms had been worsening for two weeks), psychomotor retardation, depressed mood, balance disorders, and dizziness. She had a 10-year history of follicular lymphoma. Her medical history also included an aortofemoral transplant 10 years ago, depression, removal of squamous cell carcinoma five years ago, and a recent (three weeks prior) COVID-19 infection. Systemic connective tissue diseases, neuroborreliosis, onconeuronal antibodies, antibodies against surface receptors, antibodies against aquaporin, and anti-MOG were excluded. Cerebrospinal fluid analysis was

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normal: protein 24.0 mg/dL, glucose 60.2 mg/dL, and normal cell count and IgG levels. CSF was not tested for the presence of JCV-DNA. No antibodies against aquaporin 4, oligodendrocytes, or myelin proteins were detected in the cerebrospinal fluid, and no antibodies against surface antigens were found (NMDA, AMPA1, AMPA2, GABA B, CASPR2, LGI1, DPPX). CT of the head revealed a hypoattenuating lesion in the subcortical white matter (Fig. 1A). In MRI of the head, an extensive FLAIR/T2 hyperintense focus located in the white matter of the right frontal lobe caused a slight mass effect (Fig. 1B). MRI and CT scans showed asymmetrical pathological areas of hyperintense signal in T2-weighted images and hyperintense signal in T1-weighted images. These pathological areas were located in the white matter of both brain hemispheres, mainly subcortically, and in the deep temporal structures, corpus callosum, cerebellum, and pons. Mild periventricular leukoaraiosis was noted. The subcortical U-fibres were involved. These areas did not show contrast enhancement or mass effect, but exhibited peripheral ring and patchy diffusion restriction, particularly at their leading edge. Steroid therapy was initiated with methylprednisolone sodium succinate, followed by levetiracetam due to involuntary movements. Although there was a slight improvement in limb mobility and verbal contact, no clinically significant improvement was observed after completing steroid therapy. The patient fell asleep, and disturbances in consciousness increased. She was transferred to the ICU due to a sudden deterioration in her general condition, resulting in acute respiratory failure. Cardiac arrest occurred a few hours later.

A post mortem was performed, leading to the following diagnosis: extensive multifocal intrapulmonary infiltration of lymphoma, probably of B-cell origin; a scar from a previous myocardial infarction with moderate myocyte degeneration; passive congestion with an increased number of lymphocytes in the vessels; and blurred structure with signs of necrosis in the spleen and peripancreatic lymph node. Lymphatic infiltrates were found in the portal spaces of the liver. Colloid adenomas of the thyroid gland were also observed.

Brain samples from 10 different structures were fixed in 10% buffered formalin and embedded in paraffin. The specimens were stained with haematoxylin-eosin (H&E) and Klüver-Barrera (KB). Immunohistochemical studies were performed using antibodies GFAP, CD68, LCA, and CD45RO. For electron microscope evaluation, small fragments of brain tissue were taken from the paraffin blocks. After deparaffinisation, the material was fixed in 2.5% glutaraldehyde and post-fixed in 2% OsO4, then processed for Spurr resin embedding. Ultrathin sections were stained with uranyl acetate and lead citrate. The sections were examined with a transmission electron microscope (TEM), JEOL model 1400.

Light microscopic examination of the brain samples from the right frontal lobe revealed necrotic foci of demyelination with macrophage proliferation and opaque enlarged nuclei of oligodendrocytes. Numerous scattered partially confluent foci of demyelination were observed in the left frontal and parietal lobes, the right temporal lobe, the cerebellum, the pons, and the corpus callosum (Fig. 1C–E, G). These demyelinating lesions contained a large number of foamy macrophages, but only a few perivascular lymphocytes (Fig. 1F, H). Older demyelinating lesions contained large reactive astrocytes with bizarre pleomorphic hyperchromatic nuclei (Fig. 1I, J). Enlarged oligodendrocytes with glassy chromatin nuclei were filled with large inclusions resembling 'ground glass' (Fig. 1D). Electron microscopic examination of enlarged oligodendrocytes revealed granular intranuclear inclusions/virions of the JC polyomavirus (Fig. 1K, L).

In the differential diagnosis following ultrastructural identification of JC virions in the nucleus, the following disease entities were considered: progressive multifocal leukoencephalopathy (PML), PML-immune reconstitution inflammatory syndrome (PML-IRIS), fulminant JC encephalopathy involving cortical pyramidal neurons (JCE), JC granule cell neuronopathy (JC GCN), and JC meningitis [3–5].

The most frequently described entities in the medical literature are progressive multifocal leukoencephalopathy (PML) and PML-immune reconstitution inflammatory syndrome (PML-IRIS) [5]. In the classic form of PML, histopathological images show little or no inflammation. PML-IRIS is the same disease as PML, but with a high degree of inflammation. Neuroimaging findings in inflammatory forms of the disease include contrast enhancement, perilesional oedema, and mass effect on midline structures. Contrast enhancement suggests an inflammatory component, but the absence of enhancement does not exclude the diagnosis. In PML without signs of inflammation, MRI shows no contrast enhancement or mass effect. In PML-IRIS, demyelination may result from excessive brain tissue destruction by the host's immune system, whereas in PML demyelination is caused by JC virus-induced damage to infected oligodendrocytes [5].

Other disorders caused by the JC virus have also been described, including granule cell neuronopathy of the cerebellum (JCV GCN) and fulminant JC encephalopathy involving cortical pyramidal neurons (JCE) [3]. Dang and Koralnik (2009) suggested that JCV tropism for granule cells was associated with a 10-nucleotide deletion in the C-terminus of the VP1 gene. It is possible that other mutations in the JCV coding region may be associated with JC virus tropism for different types of neurons and neuroglial cells [6]. Cerebellar symptoms may occur in patients with JCV GCN. Neuropathological findings include cerebellar atrophy and cerebellar granule cell damage, but demyelination in the cerebellum is rarely observed. Patients with JC encephalopathy often present clinically with aphasia and global cognitive decline. Histologically, damage to cortical pyramidal neurons and astrocytes is observed in the cortex and subcortical grey matter [3].

In our case, the clinical symptoms, neuroimaging features, ultrastructural visualisation of intranuclear polyomavirus particles, and especially the neuropathological evaluation of fragments from 10 brain structures, allowed the diagnosis of

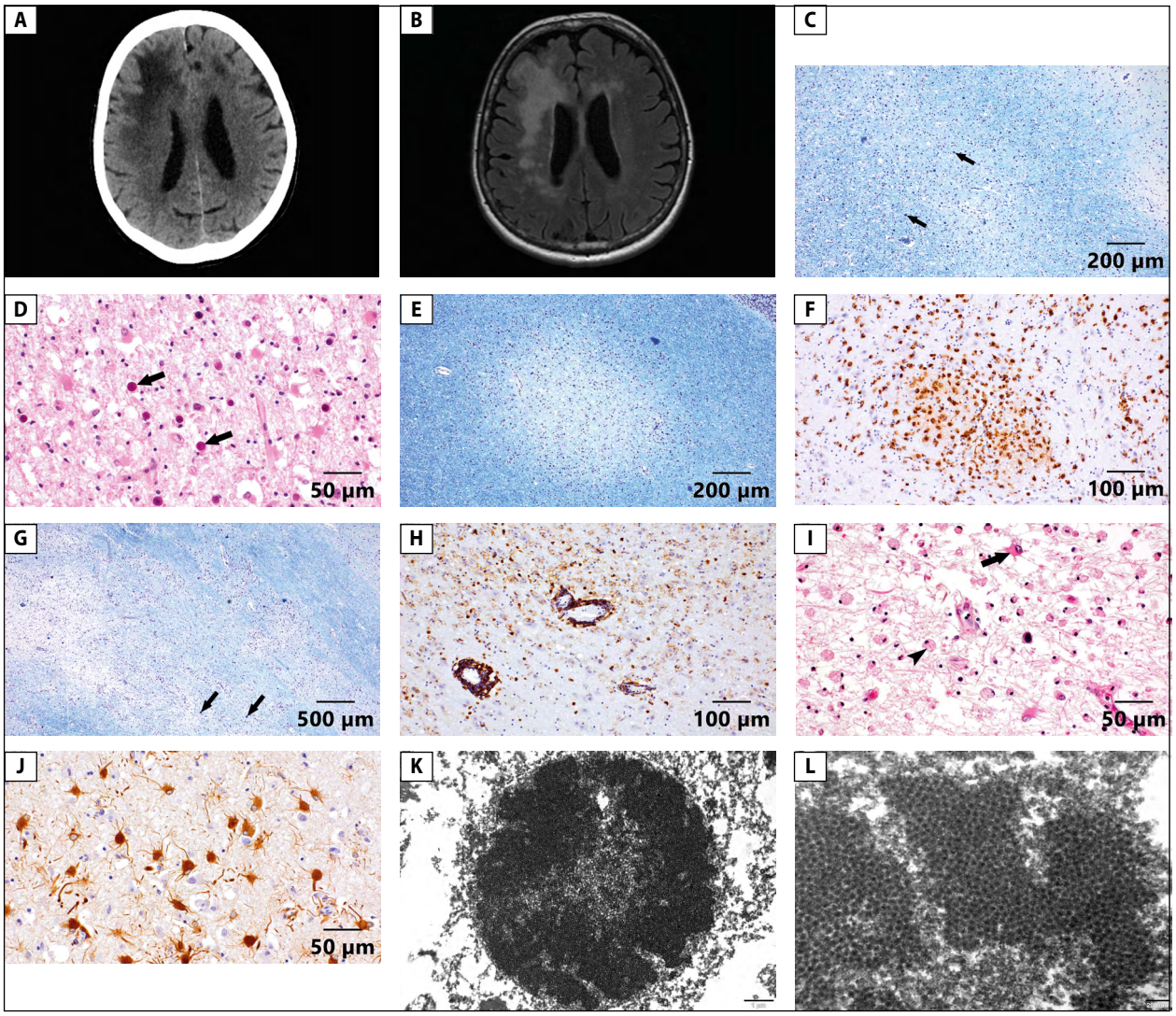

Figure 1. **A.** CT of head shows a hypoattenuating lesion in subcortical white matter. Note characteristic scalloped lateral margin; **B.** T2-weighted MRI shows a hyperintense lesion in right frontoparietal region within subcortical and periventricular white matter; **C.** Klüver-Barrera staining of frontal lobe shows areas of demyelination and enlarged oligodendrocytes (arrows); **D.** Haematoxylin and eosin staining of frontal lobe shows enlarged oligodendrocytes with 'ground glass' inclusions (arrows); **E.** Klüver-Barrera staining of cerebellum shows areas of demyelination and enlarged oligodendrocytes; **F.** Immunostaining of cerebellum with CD68 antibody shows macrophage proliferation in demyelination area; **G.** Klüver-Barrera staining of pons shows areas of demyelination and enlarged oligodendrocytes (arrows); **H.** Pons. Scanty perivascular lymphocytes. IHC CD45RO; **I.** Haematoxylin-eosin staining of frontal lobe shows macrophages (arrowhead) and atypical astrocytes (arrow); **J.** Immunostaining of frontal lobe with GFAP antibody shows large bizarre astrocytes; **K.** Electron micrograph showing granular large inclusions of JC virions in nucleus of an infected oligodendrocyte. Original magnification × 15,000; **L.** Electron micrograph showing intranuclear polyomavirus particles in PML. Original magnification × 60,000

PML. Brain biopsy, as proposed in the diagnostic algorithms for PML, seems to be helpful, but it may not be sufficient to diagnose other JC virus-related brain conditions [4].

Article information

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