

HIV-Associated JC Virus – Granule-Cell Neuronopathy (JCV – GCN) with the Hot-Cross-Bun Sign

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Abstract

Progressive multifocal leukoencephalopathy has long been described as the sole feature of JC virus (JCV) infection of the central nervous system. Over the past decade, its spectrum has extended to new forms of encephalopathy, notably affecting neurons. We describe an HIV-infected patient with worsening cerebellar symptoms, progressive cerebellar atrophy and a hot-cross-bun sign attributed to JCV–granule-cell neuronopathy (GCN), and 20 years of follow-up.

Keywords: Progressive multifocal leukoencephalopathy; Granule-cell neuronopathy; HIV; AIDS; Hot-cross-bun sign

Introduction

Progressive multifocal leukoencephalopathy (PML) remains an important complication of HIV-1/AIDS, despite widespread combined antiretroviral therapy (cART). As its name implies, it was long thought to be only a demyelinating disease restricted to brain white matter. However, JC virus (JCV), the causative agent of the classic PML form, infects glial cells and neurons, and is now known as the etiology of granule-cell neuronopathy (JCV–GCN), the productive JCV encephalopathy of cortical pyramidal neurons, and productive JCV meningitis of leptomeningeal and choroid plexus cells [1]. Histological studies demonstrated that neurons are infected more frequently than clinically recognized, especially the cerebellar granular layer [2]. Herein, we describe the particular MRI pattern of our JCV–GCN patient to alert physicians to recognize its origin and deal with it appropriately.

Case Report

In December 1994, cerebral frontal and retinal toxoplasmosis abscesses revealed HIV infection (15 CD4 cells/ μ l) in a 52-year-old man. Under anti-toxoplasma therapy, the brain abscess completely disappeared without any sequelae but low vision as a macular sequela persisted. In January 1995, he started zidovudine and lamivudine bitherapy. One month later, cerebellar kinetic syndrome-associated gait disturbance and dysarthria appeared. Brain MRI showed marked cerebellar atrophy, with no gadolinium enhancement, no visible lesion and no hot-cross-bun (HCB) sign. Normal cerebrospinal fluid (CSF) analysis (cell count, glucose and protein levels) was negative for bacteria, fungi and viruses, except for JCV-positive PCR. Laboratory test results were: normal vitamins B1, B12 and E; negative for paraneoplastic neuronal antibodies and spinocerebellar ataxia mutations; and no alcoholism. PML was suspected [3]. Neurological findings remained stable throughout 1995 and only CSF PCR JCV-positivity persisted in April 1995. After thorough reexamination in 1999 following the publication of 10 cases of HIV-infection-associated isolated cerebellar atrophy [4], only the JCV etiology persisted; CSF JCV-PCR was negative. Between 2002 and 2005, his bilateral cerebellar syndrome progressed with more pronounced gait ataxia and cerebellar atrophy on brain MRI without HCB sign. Since 2005, cART has very well-controlled his HIV (550-750 CD4 cells/ μ l and plasma virus load (PLVL) <200 copies/ml).

In December 2014, on raltegravir (800 mg/d), darunavir (800 mg/d) and ritonavir (100 mg/d), he underwent a new thorough work-up because of worsening gait ataxia: CD4-cell count: 832/ μ l; CD4/CD8 ratio: 1.15; PLVL: <20 copies/ml; truncal ataxia; bilateral cerebellar kinetic syndrome; saccadic pursuit eye movements; motor and sensory examinations: normal deep-tendon reflexes, flexor plantar response and walking without assistance; neither autonomic dysfunction nor Parkinsonism; normal electrocardiogram; brain MRI: the known cerebellar atrophy, particularly in the vermis, no lesions suggestive of PML, and an HCB sign (Figure 1); laboratory findings: normal CSF, with all viral PCRs, including JCV, negative; and normal or inconclusive vitamin E, paraneoplastic neuronal and deamidated gliadin peptide antibodies, mutations for spinocerebellar ataxias and Fragile X syndrome, anti-JCV antibody-positivity (STRATIFY JCV™DxSelect™ test, Focus Diagnostics). Neurological stability was confirmed April 2015.

Discussion

Differential diagnoses of HIV-infection-associated cerebellar involvement principally include opportunistic infections, non-Hodgkin lymphoma and metastases, paraneoplastic diseases and post-infectious immune-mediated processes [5]. The cause of the cerebellar disorder can usually be established based on clinical, radiological and CSF features with PCR. Hence, today, cerebellar biopsy is rarely needed to establish a specific diagnosis.

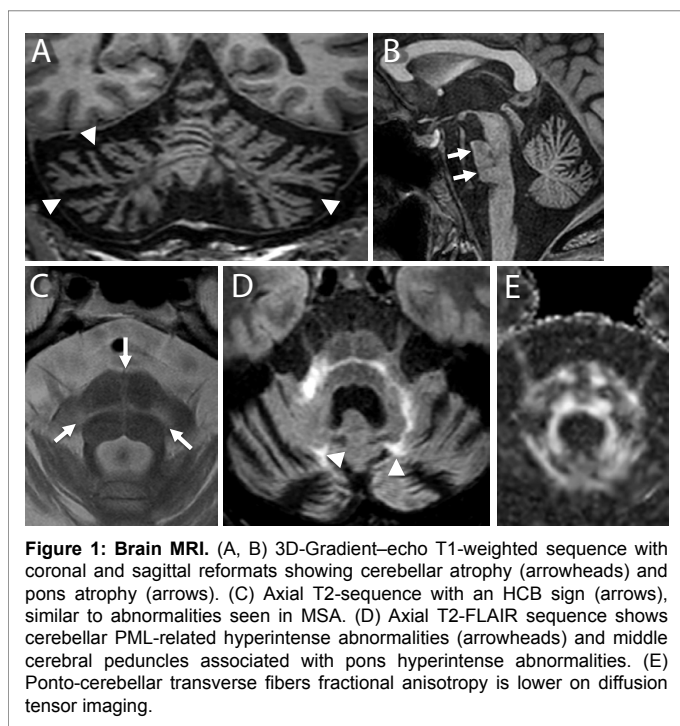
Since 1994 [3], intriguing progressive cerebellar syndromes with debilitating manifestations without direct evidence of HIV infection, opportunistic infection or malignancy, and MRI-visualized unexplained marked cerebellar atrophy have been described [4]. PCR-JCV detection in the cerebellar biopsy of one of 10 patients had

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evoked its potential role [4]. Indeed, 1993 autopsy-study results [6] demonstrating an elective JCV infection of the cerebellar GCN layer were confirmed in 2003 [7]. In 2005, Koralnik et al. coined the term JCV–GCN that defined new JCV-infection form [8].

JCV–GCN differs from classic PML and results from mutant JCV harboring a small VP1-capsid–protein deletion that shifts viral tropism from glial cells to cerebellar GCs [1,2], thereby explaining the dominant cerebellar dysfunction clinical picture. The exact mechanism(s) inducing mutations and modifying GC tropism are unknown. JCV–GCN diagnosis relies on brain MRI, visualizing marked cerebellar atrophy, and CSF analyses, showing normal cell count and protein level, but with JCV-positive PCR negative for all other infectious pathogens. JCV–GCN is sometimes associated with T2-weighted/fluid-attenuated inversion recovery (FLAIR) hyperintense white matter abnormalities typical of PML but is a distinct clinical entity [1]. Only 24 cases of HIV-associated JCV–GCN, including our patient, have been reported [9-16].

Satisfying JCV–GCN diagnosis criteria, our patient has survived 20 years [8]. In burnt-out PML, the classic histological features present in the acute-stage biopsy are absent at autopsy [17]. Virus and viral antigen are also absent in old burnt-out lesions devoid of affected oligodendrocytes [18] and 80% of long-term PML survivors having cleared JCV [19], thereby explaining our patient’s early PCR JCV-positivity and CSF JCV-PCR–negativity 20 years later. PML-progression heterogeneity has been described since the first cases and long-term survival (10%) is known since 1988 [20]. Albeit remarkable, our patient’s prolonged survival is consistent with other JCV–GCN observations [8,9,16]. Whether JCV–GCN has a better prognosis than other PML forms is unclear. Our patient probably benefited from cART-restored immunity. Another striking point of our observation is the progression of the cerebellar syndrome despite cART. This has already been observed in another published case [9]. The JCV–GCN developed and gradually progressed in this HIV-infected patient despite good HIV-control indices (undetectable PLVL and 350 CD4 cells/μl) at presentation and during his follow-up. In our patient, JCV–GCN has

probably reduced the cerebellar neuronal reserve since onset. Hence, concurrent normal age-related cerebellar cells neurodegeneration might also be an explanation to his gait worsening 20 years after the first symptoms [21].

The MRI HCB sign, characterized by cruciform T2- and FLAIR-signal hyperintensity within the pons (Figure 1), has been described in only 6 HIV-associated JCV–GCN patients [9,10,15,16]. It is said to be highly specific, but not pathognomonic, for multiple-system atrophy (MSA). Whether HCB occurs from onset or is a feature of later JCV–GCN stages is discussed. Our patient’s long radiological monitoring supports the latter hypothesis, as previously suggested [10]. GCs are a major class of cerebellar interneurons in synaptic contact with Purkinje cells. We think the HCB sign in JCV–GCN results from the progressive retrograde degeneration of the axons of various cerebellar connections, accompanying Wallerian degeneration of the pontocerebellar tracts with gliosis.

MSA was excluded because of the long follow-up without neurological deterioration and any dysautonomic sign, notably the absence of characteristic early and severe autonomic failure, i.e. no orthostatic blood pressure decrease or urinary incontinence [22]. Approximately half the patients require walking aids within 3 years after motor-symptom onset, 60% require a wheelchair after 5 years and the patient becomes bedridden within a median 6-8 years [22]. Brain MRI can also help distinguish these two entities: FLAIR cerebellar atrophy and hyperintensities are more asymmetric in JCV–GCN than in MSA, while putamen atrophy with the “putaminal rim sign” is present only in MSA [22].

Conclusion

Our case highlights JCV’s ability to infect neurons and not only glial cells, with the sole neurological feature being clinical cerebellar syndrome. As awareness of central JCV-infection types other than PML grows, this currently under-recognized JCV–GCN could become frequent in persons living with HIV (PLHs). Moreover, the HIV epidemic is entering a chronic phase in which most PLHs have life expectancies approaching general population norms [23]. Therefore, more ≥50-year-old PLHs represent the majority of all PLHs in Western countries. Perhaps because PLHs are prone to developing age-related diseases earlier or simply that they are reaching ages at which the incidences of these age-related neurodegenerative diseases are more frequent means clinicians will have to consider alternative diagnoses to HIV-related neurological consequences and aging, as recently illustrated with Parkinson’s disease [24]. Because MSA can start as a cerebellar syndrome, it will be important to distinguish JCV–GCN with HCB sign from early MSA because their treatments differ.

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