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JC virus granule cell neuronopathy: A cause of infectious cerebellar degeneration

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ABSTRACT

JC virus (JCV) infection of glial cells can lead to progressive multifocal leukoencephalopathy (PML) in immunocompromised patients. A newly described phenotype of the infection is infection of neurons. This distinct clinical and radiological syndrome is named JCV granule cell neuronopathy, characterized by exclusive or predominant cerebellar atrophy. We report the clinical and radiological longitudinal findings of 5 HIV-infected patients referred to us between September 2004 and November 2011 who exhibited JCV granule cell neuronopathy (4 probable cases and 1 possible). The association of immunocompromised status, progressive cerebellar syndrome, MRI abnormalities with cortical cerebellar atrophy and cerebrospinal fluid positive for JCV on PCR allowed for a highly probable diagnosis. The reversal of the immunocompromised status is the only way to stop the disease evolution. Motor functioning can remain impaired, but the illness itself, unlike progressive multifocal leukoencephalopathy, does not seem to threaten life.

1. Introduction

JC virus (JCV) is a small, ubiquitous DNA virus belonging to the family of human polyomaviruses. After primary infection, it establishes persistent or latent infection or both, probably in the urinary tract and bone marrow and possibly in the central nervous system (CNS) [1].

The main disease associated with JCV infection is progressive multifocal leukoencephalopathy (PML). PML results from infection of oligodendrocytes and, to a lesser degree, astrocytes, which leads to extensive and multifocal myelin breakdown and white-matter destruction. The disease most often occurs at times of severe immunosuppression caused by hematological cancers, AIDS, systemic diseases such as sarcoidosis or systemic lupus erythematosus, solid organ transplantation or, recently, immunosuppressive therapy for autoimmune diseases, such as natalizumab, rituximab, and efalizumab [2]. Classical histologic features of PML include multifocal areas of demyelination, JCV-infected oligodendrocytes with enlarged amphophilic nuclei at the periphery of lesions, reactive gliosis with enlarged, unusual astrocytes, some sustaining JCV infection, and macrophages that phagocyte myelin and cellular debris [3].

However, JCV has been identified in some human brain neurons, particularly granule cell neurons of the granular layer of the cerebellum, within the context of classical PML or in isolation within patients presenting isolated ataxia and cerebellar atrophy [4]. This distinct radiological syndrome was named JCV granule cell neuronopathy (JC-GCN) by Koralnik in 2005 [5].

The radiological aspect of JC-GCN is distinct from posterior fossa classical PML: the cerebellar and brainstem may be involved in PML associated with supratentorial white-matter disease. A retrospective radiological study of 48 histologically proven cases of PML revealed involvement of the hindbrain in up to 55% of patients [6]. The disease was restricted to the brainstem and cerebellum in 6% of this series, but the infratentorial involvement was defined as a white-matter T2 hypersignals, which was classical PML and not JC-GCN.

We report here 4 probable cases of HIV-associated JC-GCN and 1 possible case. The 4 probable cases were defined by cerebellar and brainstem progressive atrophy, no radiologic evidence of classical PML lesions, and JCV-positive cerebrospinal fluid (CSF) on PCR; and the possible case elicited the same radiological findings but JCV PCR was negative.

2. Patients and methods

We retrospectively reviewed the clinical and radiological features of 4 probable cases and 1 possible case of HIV-associated JC-GCN referred to our neurological department between September 2004 and November 2011. Inclusion criteria were previously known HIV infection or discovery at the time of the neurological symptoms; progressive clinical involvement of cerebellum and/or brainstem as defined by gait disturbance, speech difficulties, and ataxia of limbs; radiologic evidence

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of cerebellar atrophy; and positive detection of JCV DNA by PCR in CSF. Exclusion criteria were significant supratentorial-related lesions; alternative diagnosis such as cerebellar or brainstem tumor, stroke, abscess, cancer known to cause cerebellar paraneoplastic syndrome; anti-neuron antibodies; history of excessive alcohol consumption or circumstances that led to vitamin B1 deficiency. Diagnostic criteria were adapted from Cinque et al. [7]. We considered probable JC-GCN if JCV DNA was detected in CSF by PCR and possible JC-GCN as negative PCR results.

3. Results

Of the 5 patients (4 women; age range 28 to 43 years), 3 were directly admitted to our neurological department from the emergency room, 1 was referred from another hospital and 1 was referred from a remote institution by telephone. The medical and radiological charts were retrospectively reviewed systematically. Clinical, biological and radiological results of the cases are summarized in Tables 1 to 3. Four patients fulfilled the criteria of probable JC-GCN and 1 patient (patient 3) fulfilled criteria of possible JC-GCN.

Four patients had HIV-1 infection and 1 patient had HIV-2 infection. The CD4 count ranged from 20 to 396/mm^3 at the time of JC-GCN diagnosis, but patient 2, with CD4 count 396/mm^3, had started combined antiretroviral therapy (cART) in another country 9 months after the onset of the first cerebellar manifestations and was examined by us 5 months after the cART had been started, so the CD4 count was likely lower at disease onset.

No patient had received optimal cART before the clinical onset of JC-GCN, because this infection was at the beginning of HIV infection or because they were not compliant with treatment. All patients had symptoms and signs restricted to cerebellum and brainstem, except for patient 1 who had a concomitant occipital toxoplasmosis and exhibited visual seizures and patient 3 who presented paranoid delirium during the first weeks of hospitalization, supposedly as a reaction to the discovery of HIV infection.

Two patients had another concomitant opportunistic infection of the CNS: patient 1 had paroxystic visual hallucinations 2 weeks before the onset of gait disturbance. Successive MRI revealed an occipital abscess, which completely resolved with anti-toxoplasmic drug therapy, but the cerebellar syndrome worsened markedly, as did cerebellar and brainstem atrophy. Patient 5 experienced CNS cryptococcosis relapse at the onset of the cerebellar disease. Successive brain MRI revealed improvement in abscesses with anti-cryptococcic drug treatment, but cerebellar clinical and radiological signs worsened.

Patient 2 had lived in another country when the first symptoms occurred. She returned to France 14 months after the disease onset; HIV therapy was started 9 months after disease onset, 5 months before the first examination in France. We could not obtain medical data from the other country. CSF was positive for JCV DNA when she was admitted to a French hospital, 14 months after disease onset.

Patient 3 was seen in 2004. Lumbar puncture performed 3 months after disease onset was negative for JCV DNA. The retrospective examination of her medical file and the similarity with the other described cases led us to the diagnosis of possible JC-GCN.

We were able to review longitudinal evolution of MRI findings for 4 patients (Fig. 1). The first MRI for patient 2 was not available. No patient had classical PML radiological findings, as defined by white-matter T2/FLAIR and T1 MRI changes. All patients had pure infratentorial disease, with predominant atrophy (Figs. 1 and 2). At disease onset, MRI findings were normal in only 1 case, and for the other cases, the changes were so mild that they might not have been seen. Cerebellar T2 hypersignals were absent or mild but then extended from vermis and/or cerebellar hemispheres to the cerebellar peduncle and sometimes the pons. Two remarkable findings are the progressive and major cerebello-pontine atrophy: the fourth ventricle was enlarged in every patient at about 1 year after disease onset, and an axial cross appeared in the pons in 3 of 5 patients (Fig. 2). This cross looks like the "hot-cross-bun sign", previously described in multiple system atrophy (MSA) [8]. None of the patients showed radiological immune-restitution syndrome as defined on contrast enhancement after HIV therapy was started.

During follow-up, motor disability remained severe, but no patient died under HIV therapy. Two of the 5 patients were not able to walk alone. Patient 3 was hospitalized for 5 years, then was admitted to an institutional care facility. Patient 5 was still hospitalized 3 years after disease onset. No patient showed dementia.

4. Discussion

To our knowledge, this is the largest case series of JC-GCN in HIV-infected patients. One patient fulfilled only possible clinical diagnosis criteria because JCV DNA was not detected in CSF. Nevertheless, alternative diagnoses were ruled out: the case exhibited no toxic substance use, no anti-neuron antibodies, and no cancer, and after a period of disease worsening, it remained stable for 5 years, which led to ruling out a primary degenerative disease such as MSA. CSF examination was performed early, 3 months after disease onset, and was not performed again. At that time (year 2004), the sensitivity of our laboratory assay was lower than it is now. JCV DNA detection by nucleic acid amplification in HIV-infected patients has a sensitivity of 72% to 92% and increases with disease progression [7] but may be reduced, to 58%, in cART-treated HIV-infected patients [9]. In a recent review of 28 cases of PML due to natalizumab treatment in multiple sclerosis patients [10], CSF viral load was as low as ≤500 copies/mL, so a negative result does not exclude the diagnosis especially if the laboratory uses a low-sensitivity assay.

Table 1
Baseline data.

Characteristics	Patient no.				
	1	2	3	4	5
Age at JC-GCN diagnosis–sex	43–F	31–F	39–F	28–F	33–M
Time from HIV diagnosis to JC-GCN diagnosis	10 y	3 y	Inaugural	18 m	11 y
HIV serogroup	HIV1	HIV1	HIV1	HIV1	HIV2
Previous opportunistic infection	Pulm TB, PNP Cut.HSV CNS toxo			Pulm TB CNS toxo	Syphilis CNS crypto
Previous HIV therapy	Few months (poor compl)			1. ZDV–3TC–LPV/r (poor compl) 2. FPV–RTV–ddI–TDF (poor compl)	1. ZDV–3TC–NVP 2. ddI–D4T–NFV (poor compl) 3. ABC–3TC–DRV–RTV
Nadir CD4 count /mm^3	73	8	26	21	20

Abbreviations: JC-GCN: JC virus granular cell neuronopathy; m: month; y: year; pulm TB: pulmonary tuberculosis; Cut.HSV: cutaneous Herpes Simplex Virus infection; PNP: infectious pneumopathy; CNS toxo: cerebral toxoplasmosis; CNS crypto: central nervous system cryptococcosis.
anti-HIV treatment: RTV: ritonavir; FTC: emtricitabine; TDF: tenofovir; ATV: atazanavir; FPV: fozamprenavir; ddI: didanosine; ZDV: zidovudine; 3TC: lamivudine; LPV/r: ritonavir + lopinavir; NVP: nevirapine; ddI: didanosine; D4T: stavudine; NFV: nelfinavir; poor compl: poor compliance to treatment.