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Heterogeneous imaging characteristics of JC virus granule cell neuronopathy (GCN): a case series and review of the literature

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Abstract Granule cell neuronopathy (GCN) is a rare JC virus (JCV)-related disease in immunocompromised patients, characterized by lytic infection of the cerebellar granule cell layer. To enable early diagnosis and intervention, we identify features of GCN and describe possible aspects of disease heterogeneity. We report on two new cases of GCN in HIV-infected patients of whom we retrospectively assessed clinical and radiologic data. In addition, we carried out a literature search and review of clinical, radiologic and histopathologic findings of all published GCN cases. Including the two new cases reported here, a total of 18 GCN cases were included in this study. HIV infection, present in 12 of the cases, was the most common underlying condition, followed by monoclonal antibody treatment which was present in three cases. Cerebellar atrophy was detected in all except two cases. In 12 patients a heterogeneous distribution pattern of white matter changes in the cerebellum and brainstem was observed. Imaging findings in GCN are remarkably heterogeneous; exhibiting cerebellar atrophy, as well as white matter pathology, particularly in the adjacent infratentorial white matter. This suggests an overlap of GCN with other JCV-related diseases, such as progressive multifocal leukoencephalopathy.

Keywords JC virus · Granule cell neuronopathy · HIV · Magnetic resonance imaging · Cerebellar atrophy · Progressive multifocal leukoencephalopathy

Introduction

The JC virus (JCV) is a neurotropic polyoma virus first described in the 1970s [1]. After primary infection, JCV establishes a latent and persistent infection in a variety of tissues such as tonsils, kidneys and the human gut and shows constant or periodic replication in some tissues, for instance in the epithelium of the urinary tract. Seroprevalence studies indicate that between 30 and 70 % of individuals are seropositive and seroprevalence increases with age [2]. JCV reactivation occurs frequently in immunocompetent and immunocompromised patients. In immunocompromised patients, JCV may cause a lytic infection of white and grey matter cells of the central nervous systems (CNS). Several JCV-associated diseases have been described, including progressive multifocal leukoencephalopathy (PML), JCV encephalopathy, JCV meningitis and JCV granule cell neuronopathy (GCN) [3].

PML is the most common JCV-associated disease, which is characterized by a lytic infection of oligodendrocytes, astrocytes and neurons, ultimately leading to demyelination and neuronal damage [4]. Most of the knowledge about PML in terms of clinical presentation, imaging characteristics, and prognosis, has been derived

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from human immunodeficiency virus (HIV)-infected patients. This was especially the case in the pre-highly active anti-retroviral therapy (HAART) era. However, in the past few years other conditions have been associated with PML, including treatment with monoclonal antibodies for autoimmune diseases, such as natalizumab in relapsing multiple sclerosis [5]. Due to its high sensitivity in the detection of PML pathology—even before the onset of clinical symptoms—brain magnetic resonance imaging (MRI) has been incorporated into PML diagnostic criteria and is currently recommended as a screening tool in surveillance programs of immunocompromised patients [6]. Despite its high sensitivity, it has been conclusively demonstrated in monoclonal antibody (e.g., natalizumab) associated PML that MRI findings, particularly at early stages of the disease, are heterogeneous and fluctuating [7–9].

More recently, other JCV-associated disease entities have been described in which lytic infection predominately occurs in grey matter cells. Amongst these, GCN is characterized by a selective infection of the granule cell neurons in the cerebellum, leading to neuronal loss and gliosis and cerebellar atrophy [10]. As in PML, most of the GCN cases have been described in HIV-infected patients [11–16]. However, GCN is even rarer than PML. Recent case reports have also documented GCN in patients treated with monoclonal antibodies, such as rituximab and natalizumab [17–19]. MRI is able to detect GCN related imaging findings such as cerebellar atrophy in GCN patients. In addition to neurodegenerative changes of the cerebellum, white matter changes have been described in GCN patients. This has led to a discussion on whether GCN is a separate disease entity, or just a PML variant with predominant cerebellar grey matter involvement [11, 13, 14, 17, 19–24]. Knowledge about the imaging findings of GCN is crucial to facilitate an early diagnosis. However, the imaging characteristics of all published GCN cases have not been systematically reviewed to date.

The aim of this study is to describe two additional cases of HIV GCN and review the literature in terms of underlying clinical conditions, histopathology and imaging findings in GCN patients.

Patients and methods

Case series

We retrospectively reviewed the medical records and serial imaging files of two HIV-associated GCN patients who were admitted to our clinic, with adherence to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Literature review

In order to identify all reported GCN cases, we searched the NCBI PubMed database using the search terms: "granule cell neuronopathy", "granular cell neuronopathy", "cerebellar JC virus" and "JC virus cerebellum". This yielded 109 potentially relevant articles. Papers in which both clinical presentation and imaging findings were described in sufficient detail were included. The reference sections of included articles were searched as well. The clinical information, histopathology (if available) and the imaging characteristics of each case were assessed.

Results

Case series

Case 1

A 45-year-old HIV-positive man presented with a 3-month history of gait instability of sub-acute onset. He had been seropositive for HIV for 10 years and HIV viral load was undetectable in plasma at the time of presentation. His treatment regimen consisted of efavirenz, tenofovir and emtricitabine and his absolute $CD4^+$ T cell count fluctuated around 350 cells/mm^3. His medical history revealed type 2 diabetes, hyperthyroidism and acute lymphoblastic leukemia for which he had been treated with various chemotherapies, as well as intrathecal methotrexate, cytarabine and dexamethasone. This had resulted in complete remission for the previous 5 years. There was no history of drug use or alcohol abuse.

At presentation, the neurological examination showed cerebellar gait disturbances with a positive Romberg test. In addition, the patient displayed non-fluent pursuit eye movements without nystagmus and decreased light touch sensation in the lower extremities. The finger–nose and heel–knee–shin movements were performed normally and there was no dysdiadochokinesia. Cognitive, motor and speech examinations were normal and deep tendon reflexes were symmetrically low with flexor plantar responses.

MRI of the brain and spinal cord showed marked cerebellar atrophy, in particular of the vermis, with no gadolinium enhancement or signs of PML or myelopathy (Fig. 1a–e). CSF analysis revealed a normal cell count and normal glucose and protein levels with negative tests for *Borrelia* and syphilis. Laboratory testing showed normal vitamins B_{12} and E and paraneoplastic neuronal antibodies (including anti-Hu, anti-Yo, anti-Ri, anti-Tr, anti-amphiphysin, anti-CV2 and anti-Ma2) were negative. EMG showed no evidence of polyneuropathy. Mutation analysis
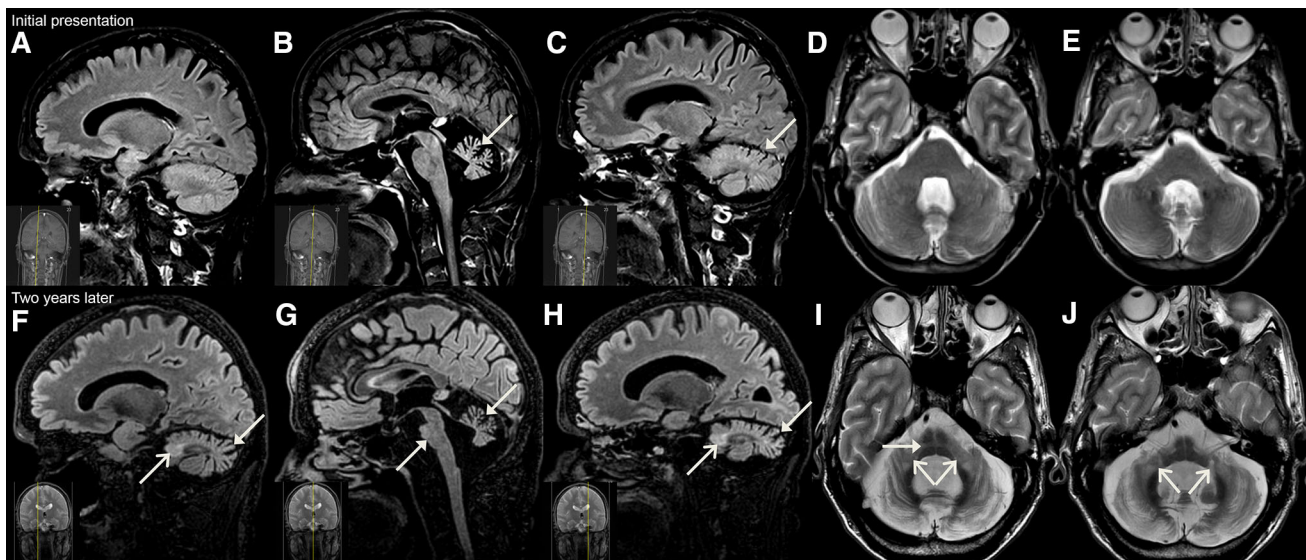
Fig. 1 MRI obtained from case 1 at the initial presentation (*upper row*, **a–e**) and 2 years later after clinical decline (*bottom row*, **f–j**). Sagittal FLAIR MR images (*top row*, **a–c**) showed mild cerebellar atrophy in the lateral cerebellar hemispheres and already pronounced atrophy at the level of the vermis (*closed head arrows*). The neurodegeneration progressed substantially during follow-up, with severe atrophy 2 years after the initial presentation. In addition to the neurodegeneration, white matter changes were observed in the atrophic middle cerebellar peduncles visible on the sagittal FLAIR and axial T2-weighted MR images (*open head arrows*, *bottom row*, **i**, **j**), not visible at the initial presentation (*top row*, **d**, **e**). Please note also the severe atrophy of the brain stem, particularly of the pons (*closed head arrow*, *bottom row*, **g**) with a "hot cross bun sign" on the T2-weighted MR images (*closed arrow*, *bottom row*, **i**)

for both Friedreich's ataxia and spinocerebellar ataxias (SCA) 1, 2, 3, 6 and 7 turned out negative.

During follow-up, his unsteady gait worsened and he became wheelchair bound. Upon examination 7 months after presentation, his truncal balance was disturbed and the heel–knee–shin movements were ataxic. Brain MRI showed progressive cerebellar atrophy with new symmetric T2 high signal-intensity lesions in both middle cerebellar peduncles and the transverse pontine fibers (Fig. 1). As these changes in the pons have been described as the "hot cross bun sign" in multiple system atrophy (MSA) patients (Fig. 1f–j), MSA was considered. However, due to the absence of autonomic failure MSA seemed very unlikely. Qualitative PCR for JCV in CSF was positive in three separately obtained samples and the diagnosis JCV GCN was made.

In spite of six cycles of cidofovir, his condition gradually worsened and his speech became affected. He died 4 years after the onset of his complaints due to an unknown cause. No post-mortem examination was performed.

Case 2

A 47-year-old man, in whom HIV infection had been diagnosed 23 years before, presented with progressive drowsiness and an unsteady gait since 1 year. Walking had become increasingly difficult during the final days before admission. In addition, he had increasingly frequent headaches and reported difficulty in speaking. On examination, he was somnolent, bradyphrenic and disoriented in time. There was a marked truncal ataxia, which precluded unsupported standing and he displayed saccadic pursuit eye movements. There was dysdiadochokinesia (left more than right) but finger–nose and heel–knee–shin movements were normal. Motor and sensory examinations and deep tendon reflexes were normal with flexor plantar responses.

His medical history revealed migraine, alcohol abuse and post-encephalitic epilepsy after a smallpox vaccination as an infant for which he used valproic acid, carbamazepine and clonazepam. Although he had been noncompliant with his combination anti-retroviral therapy (cART) medication since 1 year (1 month before admission his absolute $CD4^+$ T cell count was 40 cells/mm^3), he had restarted his cART medication 3 weeks before admission.

Brain MRI showed diffuse symmetric atrophy of the cerebellum with adjacent white matter hyperintensities suggestive of gliosis or white matter infection (Fig. 2). CSF analysis showed a normal cell count and normal glucose and protein levels. Qualitative PCR analysis of the CSF was positive for JCV, confirming the diagnosis JCV GCN.

During admission his complaints decreased and, with physiotherapy, his walking improved. On follow-up 6 weeks later his walking, speaking and bradyphrenia had

Fig. 2 MRI obtained from case 2 at initial presentation. Axial FLAIR (**a**, **b**), axial T2-weighted (**c**) and sagittal FLAIR (**d**, **e**) MR images, showing pronounced atrophy of both cerebellar hemispheres (*closed head arrow*) with adjacent white matter changes (*open head arrow*)
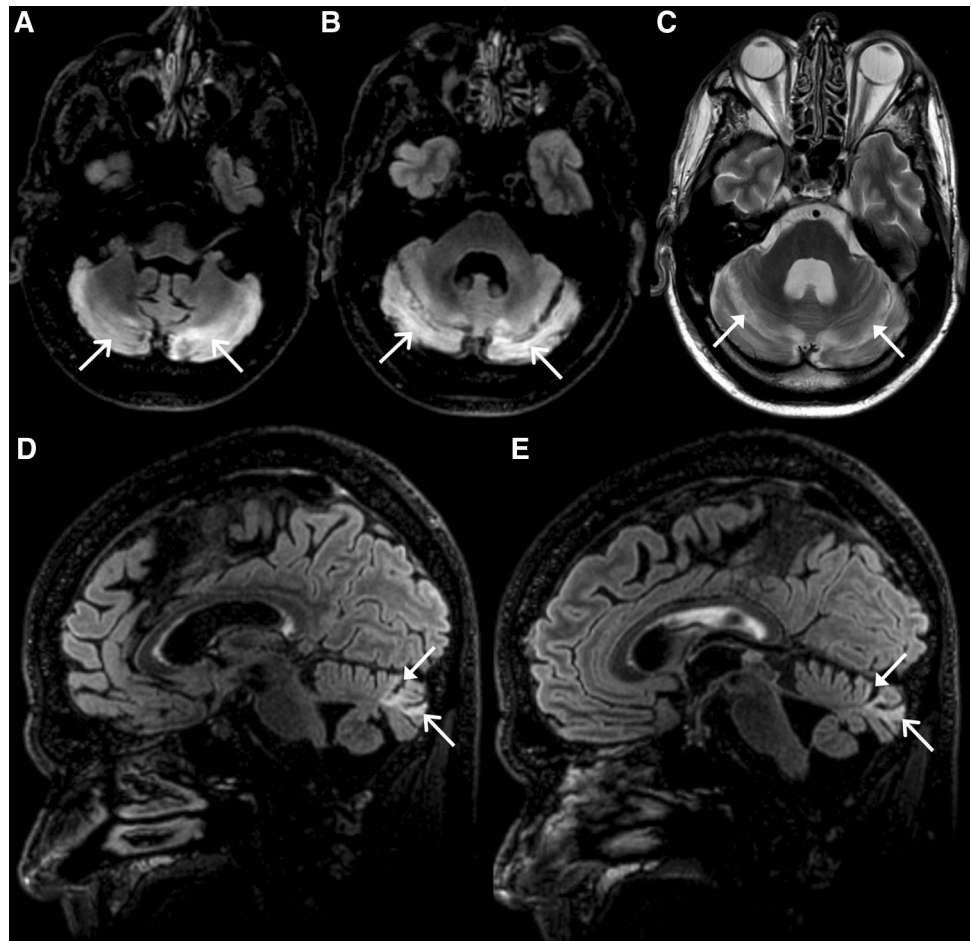
further improved. His absolute CD4$^+$ T-cell count had increased to 230 cells/mm^3 1 month after admission.

Literature review

We retrieved information on a total number of 16 cases diagnosed with GCN [10–24]. In addition, five other HIV-related GCN cases were identified, but as no information on clinical presentation, imaging findings or histopathology were given, we excluded them from this review [25].

Table 1 presents a summary of these 16 cases, plus the two additional cases presented in this report, detailing the underlying clinical condition, imaging findings and histopathology, if available. Twelve patients had HIV, which made it the most common underlying clinical condition, and three patients were using monoclonal antibodies (2 natalizumab and 1 rituximab). Cerebellar atrophy, observed in all but two cases (patients 3 and 13, Table 1), was the most consistent feature on imaging [14, 22]. Another common imaging finding, observed in 12 of the patients, was white matter abnormalities of the cerebellum and brainstem. In six of the seven cases with data available

on histopathology, evidence was present of infection of the granule cell neurons in the cerebellum with subsequent loss of the internal granule cell layer. However, in four of the seven patients, white matter changes with JCV-infected or abnormal glial cells were observed.

Discussion

In 2003, Du Pasquier and colleagues described the first case of an HIV-infected patient presenting with PML in both frontal lobes and severe atrophy of the cerebellum. On histopathology, multifocal loss of internal granule cell layer due to JCV-infected granule cell neurons was observed leading to the term granule cell neuronopathy (GCN). Since then, 17 additional cases diagnosed with GCN have been described (see Table 1 for summary of all GCN cases published to date) [10–25].

Infection and loss of the granule cell neurons are the leading histopathological features in these patients. However, in four of the seven patients, JCV-infected or abnormal glial cells were also observed. This suggests that

Table 1 All reported JCV GCN cases with radiologic and histopathological findings

Case no.	References	Age	Gender	Clinical condition	Imaging findings[a]	Histopathology cerebellum
1	Du Pasquier et al. [10]	39	M	HIV	Mild, bilateral cerebellar atrophy (left > right) without cerebellar white matter lesions. PML in frontal lobes. No gadolinium enhancement	Autopsy: multifocal and confluent foci of cell loss in IGCL with JCV-infected granule cell neurons, overlying Purkinje cells were preserved. Normal cerebellar WM
2	Koralnik et al. [13]	43	F	HIV	Moderate cerebellar atrophy without WM hyperintensity and mild cerebral atrophy. Scattered areas of signal hyperintensity in right cerebellar hemisphere and adjacent brainstem 11 months after presentation	Stereotactic needle biopsy: focal granular cell layer depletion with preserved Purkinje cells and WM 1 month after presentation. JCV PCR positive in granule cell neurons
3	Otis and Moral [14]	52	F	HIV	Abnormal signal intensity pons and right cerebellar hemisphere	Cerebellar biopsy: demyelination and JCV-infected IGCL, pleomorphic astrocytes and enlarged oligodendroglial nuclei
4	Hecht et al. [21]	15	M	CD-40 ligand deficiency	Progressive cerebellar atrophy, areas of FLAIR hyperintensity in cerebellar cortex and diffuse FLAIR hyperintensity in cerebellar WM extending into pons, consistent with transneuronal degeneration secondary to cerebellar cortical injury. No contrast enhancement	NA
5	Shin et al. [15]	37	F	HIV	Prominent cerebellar atrophy without WM lesions	NA
6	Bustamante et al. [11]	37	M	HIV	Cerebellar atrophy. WM lesions in stem, thalamus and both cerebral hemispheres	NA
7	Granot et al. [20]	49	F	Sarcoidosis	T2 hyperintense lesion in left cerebellar hemisphere and peduncle, with atrophy. 4 weeks later extending to right cerebellar hemisphere and brainstem (with hot-cross-bun sign). No contrast enhancement, not apparent on DWI	Stereotactic cerebellar biopsy: demyelination in cerebellar WM with foamy macrophages, relative preservation of axons, bizarre astrocytes and enlarged oligodendroglial cells with nuclear inclusions. JCV-infected IGCL, with abnormal nuclei, and oligodendrocytes
8	Tan and Brew [16]	42	M	HIV	Significant cerebellar atrophy without T2 changes or contrast enhancement	NA
9	Shang et al. [24]	58	F	HIV and hyper-IgE	Severe cerebellar atrophy. FLAIR and T2 hyperintensity bilateral middle cerebellar peduncles, restricted on DWI, but not on apparent diffusion coefficient. No T1 hypointensity or gadolinium enhancement	NA
10	Roux et al. [23]	38	M	HIV	Prominent cerebellar atrophy involving midline and hemispheric structures with an enlarged fourth ventricle. Mild generalized cerebral atrophy. Few white matter abnormalities on FLAIR	Autopsy: loss of granular neurons with sparing of the Purkinje and molecular layers. Severe WM lesions with enlarged bizarre astrocytes and enlarged oligodendrocyte nuclei. IHC positive for JCV in astrocytes and oligodendrocytes
11	Dang et al. [12]	25	F	HIV	Right cerebellar atrophy, no "PML lesions" in cerebellum	NA
12	Dang et al. [12]	34	F	HIV	Isolated cerebellar atrophy	NA

Table 1 continued

Case no.	References	Age	Gender	Clinical condition	Imaging findings[a]	Histopathology cerebellum
13	Keith et al. [22]	74	M	Sarcoidosis and idiopathic leukopenia	Progressive left middle cerebellar peduncle signal change without contrast enhancement or diffusion restriction	Autopsy: numerous confluent foci of myelin pallor throughout pons (incl. large focus in left middle cerebellar peduncle), medulla and cerebellum. Granule neuron depletion and intense gliosis in cerebellar cortex with relative sparing of Purkinje and molecular layers. ISH positive for JCV in granule neurons and glia of cerebellar WM
14	Schippling et al. [18]	33	F	Natalizumab therapy in MS	Atrophy of vermis and cerebellar hemispheres without T2 hyperintensities or gadolinium enhancement	Cerebellar biopsy: near-complete granule cell layer neuron loss sparing Purkinje cells. JCV infection of remaining IGCL. Signs of IRIS
15	Dang et al. [17]	Older[b]	M	Rituximab therapy in rheumatoid arthritis	Progressive cerebellar volume loss, beginning with early vermian atrophy, and T2 hyperintensity in dorsal midbrain, pons and cerebellar peduncles (with hot-cross-bun sign)	NA
16	Agnihotri et al. [19]	32	M	Natalizumab therapy in MS	Progressive cerebellar atrophy without any confluent white matter lesions. Later hyperintense lesions in the pons and cerebellar peduncle on FLAIR imaging and contrast enhancement within the cerebellum developed, suggestive of IRIS	NA
17	This publication	45	M	HIV	Progressive cerebellar and pontine atrophy (with hot-cross-bun sign), and symmetrical white matter lesions in cerebellar peduncles	NA
18	This publication	47	M	HIV	Diffuse symmetrical cerebellar atrophy with gliosis	NA

JCV JC virus, IGCL internal granule cell layer, PML progressive multifocal leukoencephalopathy, WM white matter, DWI diffusion weighted imaging, FLAIR fluid attenuated inversion recovery, IHC immunohistochemistry, ISH in situ hybridization, MS multiple sclerosis, IRIS immune reconstitution inflammatory syndrome

a Based on published information and our own interpretation of published imaging materials in figures

b Specific age not specified

GCN is—at least in a considerable number of patients—not an exclusive grey matter disease as GCN may also affect white matter structures, which is supported by the imaging findings. The most consistent imaging finding in all GCN patients, including the two hereby presented patients, is atrophy of the cerebellum suggestive of neurodegeneration. However, in two-thirds of the cases additional white matter changes in the cerebellum and brainstem, particularly in the middle cerebellar peduncles and the pons, were observed. The underlying pathology of these accompanying white matter abnormalities is not well understood. In some histopathologically confirmed cases there is evidence of infection in astrocytes and oligodendrocytes. In other cases, white matter changes, particularly in the periphery of the cerebellar hemispheres and the cerebellar peduncles, might be secondary to pronounced grey matter loss, suggestive of gliosis. This latter phenomenon can also be observed in other neurodegenerative diseases showing severe focal atrophy, such as frontotemporal lobar degeneration (FTLD) with severe focal atrophy of the frontal and temporal lobes [26, 27].

Another interesting observation in one of our patients (case 1), which has been observed in two cases reported in the literature (patients 7 and 15, Table 1) [17, 20], is the involvement of the pons with linear white matter hyperintensities similar to those seen in patients with MSA, but also in other diseases including PML, coining the term "hot cross bun sign" [28–31]. It remains unclear whether these white matter changes in GCN patients occur from the beginning, or are features of later stages of the disease. However, in case 1 presented in this study, white matter involvement in addition to severe progression of focal atrophy of the cerebellum, also affecting the brain stem, was a feature of the advanced stage of the disease. In an immunocompromised patient with infratentorial white matter lesions and cerebellar atrophy on MRI suggesting GCN, it can be challenging to decide whether these lesions represent infratentorial PML with simultaneous neurodegenerative changes of the cerebellum, or should be classified as GCN with secondary white matter involvement. Indeed, patients with infratentorial PML can show imaging characteristics comparable to GCN with accompanying white matter lesions, and may even show JCV-infected granule cells on histopathology [7, 9, 32–35].

Interestingly, in contrast to PML associated with monoclonal antibody therapy, signs of inflammation such as contrast enhancement, have not been reported in GCN patients at presentation [36, 37]. However, one patient with natalizumab-associated GCN did show contrast enhancement at immune reconstitution syndrome (IRIS) stage (patient 16, Table 1) [19]. Given the simultaneous presence of grey matter and white matter pathology in most of the GCN patients, and the observation that GCN can occur in addition to PML lesions [10, 11], it remains unclear whether GCN has to be considered as a separate entity of JCV-related disease, or a PML subtype with pronounced grey matter involvement including the cerebellar granule cells. The association of GCN with certain mutations of the JCV (located in the VP1 C terminus region of the viral DNA) supports the hypothesis of GCN as a separate disease entity [12, 38]. However, preliminary histopathological data show that granule cells are frequently infected by JCV in PML patients, which suggests that GCN is rather a PML variant—at least in a considerable number of patients [39]. This coincidence of PML and GCN was also present in two GCN cases (patients 1 and 6, Table 1) [10, 11].

A similar phenomenon of a more selective grey matter involvement can be observed in JCV encephalopathy— another JCV-related disease characterized by a predominant infection of cortical pyramidal neurons [40]. However, similar to the frequent involvement of granule cells in PML, an involvement of cortical grey matter—particularly of cortical neurons—can also be observed in PML patients. This calls into question whether JCV encephalopathy is a separate disease entity [41]. Occasionally, the cortical grey matter involvement can be the predominant and leading imaging feature in PML, suggesting a cortical phenotype of PML in some patients and stressing the fact that cortical demyelination and even neuronal infection is a relatively frequent phenomenon in PML [4, 7, 42].

Finally, it is important to note that, similar to PML, GCN may occur not only in HIV patients. Other clinical conditions associated with immunosuppression, such as immunosuppressive therapy with monoclonal antibodies such as natalizumab and rituximab may also lead to GCN [17–19]. As the arsenal of immunosuppressive drugs is constantly growing, more patients with JCV-related diseases might be expected in the near future [35, 43]. Therefore, GCN should be considered in the context of drug surveillance programs to detect opportunistic infections in an early stage. The diagnosis of GCN is challenging since the combination of cerebellar symptoms and cerebellar atrophy has a broad differential diagnosis, even in immunocompromised patients. Knowledge of the broad spectrum and heterogeneity of clinical presentations and imaging characteristics of GCN is crucial in order to enable early diagnosis and intervention by immune reconstitution, which is presumably associated with a more favorable functional outcome.

Conclusion

We show that GCN may present with heterogeneous imaging features, thereby complicating an accurate diagnosis. The most characteristic imaging feature is

cerebellar atrophy, which often occurs in combination with white matter changes in the cerebellum and brainstem. Due to the increasing number of patients treated with new generations of immunosuppressive drugs such as monoclonal antibodies and fumarates, a substantial increase of additional cases of GCN could be on the horizon. Therefore, we consider that there is a need for dedicated diagnostic criteria for GCN, which should include imaging characteristics such as cerebellar atrophy with possible concomitant white matter changes in the cerebellum and brainstem.

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