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LETTER TO EDITOR

Granule Cell Neuronopathy in a Patient with Common Variable Immunodeficiency

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To the Editor,

The JC virus or John Cunningham virus is a member of the polyomavirus family found only in humans. Initial infection occurs mainly in childhood, and is usually asymptomatic. The virus establishes lifelong latent infection in a range of tissues, including the brain. JC virus is recognised as the cause for progressive multifocal leukoencephalopathy (PML), an often-devastating central nervous system infection resulting from reactivation of latent virus, almost exclusively seen in immunosuppressed patients. Whereas PML results from JC virus infection of brain glial cells, infection of granule neurons in the cerebellum results in granule cell neuronopathy (GCN). We report a common variable immunodeficiency (CVID) patient who developed GCN, and who clinically improved with mirtazapine and mefloquine.

The patient was referred in 2004 at 58 years of age with a 5-year history of recurrent bacterial pulmonary and sinus infections and recurrent diarrhoea. Past medical history included seronegative arthritis in his twenties treated with penicillamine which had remitted after 5 years. Initial assessment for recurrent infections revealed low IgG (4.1 g/L) and IgA (0.2 g/L) with normal IgM (0.8 g/L). Specific antibody responses to tetanus, diphtheria and pneumococcal vaccination were absent. Lymphocyte subsets showed reduced CD3 + CD4+ T cells to 320 cells/μL, CD19+ B cells to 30 cells/μL and CD56+ NK cells to 3 cells/μL with normal CD8+ T cells at 818 cells/μL (Table S1 supplementary data). Human immunodeficiency virus (HIV) testing by polymerase chain reaction (PCR) was negative. Computed tomography (CT) chest showed granulomas and mild bronchiectasis in both lower lobes not previously known (Fig. S1 supplementary data). He commenced intravenous immunoglobulin (IVIg) at 0.4 mg/kg with normalisation of IgG (7.6 g/L) and resolution of respiratory infections but ongoing diarrhoea. Repeated stool cultures were negative; upper and lower gastrointestinal endoscopies were unremarkable and there was no benefit with empiric giardia therapy. He developed a sigmoid volvulus July 2010 which was resected showing only early ischaemic changes. Repeat cultures and PCR (including norovirus) were negative. Repeat lymphocyte subsets showed reduced CD3 + CD4+ T cells at 408 cells/μL and CD19+ B cells at 36 cells/μL with reduced CD27 + IgM-class switched memory B cells at 2%. He remained well on IVIg until mid-2014 when he developed lower limb weakness. Clinical examination in September 2014 revealed normal cranial nerves, normal upper limb power but mild weakness of hip abduction and moderate weakness of ankle dorsiflexion and plantar flexion. Upper limb reflexes were brisk, with preserved lower limb reflexes. Sensory examination was normal and there were no cerebellar findings. The creatine kinase was mildly elevated at 365 U/L. An electromyogram (EMG) was suggestive of mild chronic myopathy, and a muscle biopsy showed mild granulomatous inflammation. He was commenced on oral prednisolone 50 mg for presumed granulomatous myositis. There was initial improvement in weakness but he developed progressive ataxia and dysarthria. Cranial magnetic resonance imaging

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(MRI) showed cerebellar vermis and hemisphere volume loss with increased signal in the cerebellum and mild cerebellar atrophy (Fig. 1), with normal brainstem and subtle posterior fossa enhancement. Cerebrospinal fluid (CSF) examination showed mild elevation of the CSF protein 0.39 g/L (0.08–0.32 g/L), normal glucose 3.2 mmol/L (2.2–3.9 mmol/L), 0 leucocytes/μL and 1080 erythrocytes/μL. PCR on CSF was negative for cytomegalovirus, Epstein Barr virus, varicella zoster, herpes simplex virus, human herpes virus-6, enterovirus and measles virus. JC virus DNA was detected in both CSF and urine by PCR directed against the large tumour antigen coding region. It was typed as genotype 3a by sequencing of the 355 amino acid VP1 region viral DNA in both CSF and urine. The sequences were identical across 139 amino acids and did not contain deletions previously detected in several GCN-associated JC viruses. Anti-neuronal antibodies and CT of chest and abdomen were unremarkable. At this stage, he had clinically deteriorated, and was wheelchair bound with significant dysarthria. Given the positive JC virus PCR with progressive cerebellar ataxia, MRI features of cerebellar cortical atrophy with middle cerebellar peduncle signal abnormality, and history of immunodeficiency, a diagnosis of GCN was made. Prednisolone was stopped and he commenced mefloquine 250 mg weekly and mirtazapine 15 mg and remained on IVIg at a dose of 0.45 mg/kg. Clinically, on this treatment, he stabilised and has improved over the subsequent 3 years. He is now mobilising with a frame and has improved clarity of speech although remains dysarthric. Repeat MRI 3 years after presentation showed severe global atrophy of the cerebellum and pons with diffuse cerebellar white matter signal abnormality consistent with gliosis (Fig. 1). A subsequent T and B cell exome panel identified a identified a heterozygous variant in TNFRSF13B (c.579C > A; p.C193X) considered as associated with, rather than causative of CVID.

Infection of granule cell neurons with JC virus was initially identified in a HIV positive patient with PML and severe cerebellar atrophy, with infection isolated to granule cells only subsequently described in a HIV-positive patient leading to the term granule cell neuronopathy (GCN). Since infection results in the destruction of granule cells, patients present with typical signs of cerebellar dysfunction including ataxia, dysarthria and incoordination. Whilst the gold standard for diagnosis is histological evidence of lytic JC virus infection of granule cells on brain biopsy, in the appropriate clinical and radiological setting GCN may be diagnosed by detection of JC virus DNA in CSF [1].

As in PML, most cases of GCN have been described in HIV-positive patients although increasing cases related to iatrogenic immunosuppression are being described. Only a

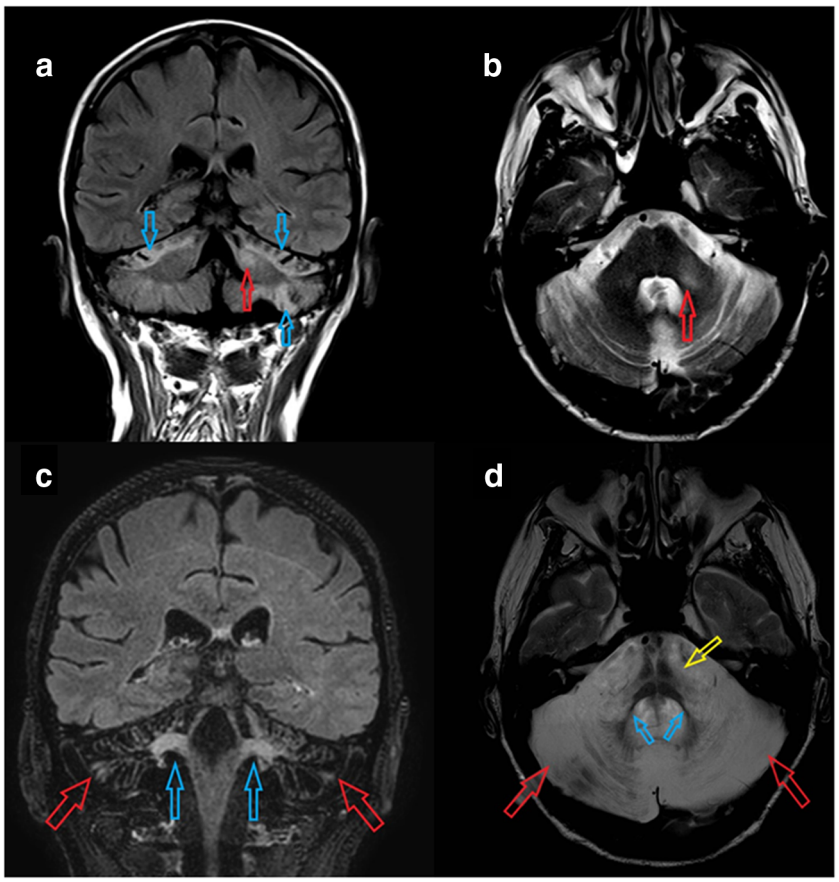

Fig. 1 **a** Coronal fluid attenuated inversion recovery (FLAIR) MRI shows bilateral cerebellar cortical atrophy and increased signal (blue arrows). Increased signal can also be seen in the left middle cerebellar peduncle (red arrow). **b** Axial T2-weighted fast spin echo (FSE) MRI shows increased signal in the left middle cerebellar peduncle (Red Arrow). **c** Coronal fluid attenuated inversion recovery (FLAIR) MRI and **d** axial T2-weighted fast spin echo MRI sequences performed 3 years after presentation show gross cerebellar atrophy (red arrows) with accompanying signal change and atrophy of middle cerebellar peduncles (blue arrows) and pontine atrophy with "Hot Cross Bun" sign indicating degeneration of transverse pontocerebellar fibres (yellow arrow)

single case of GCN in a primary immunodeficiency patient has been described [2]. A 15-year-old patient on replacement IVIg for CD40 ligand deficiency (although details of CD40L diagnosis were not given) presented with typical cerebellar signs and JC virus infection. He had no benefit with intravenous cidofovir or high-dose IVIg. At 7-month follow-up, he had progressive decline of cerebellar function with sparing of cognitive function and died at 23 months. Since PML has been described in various primary immunodeficiencies including STAT1 gain of function, X-linked agammaglobulinaemia and DOCK8 deficiency [3], it is likely other primary immunodeficiency patients are also prone to GCN. GCN shows significant heterogeneity in radiological features with the most consistent finding cerebellar atrophy suggestive of neurodegeneration, but additional white matter changes in the brainstem and cerebellum are commonly seen [4]. Our case demonstrated associated cerebellar cortical contrast enhancement and true diffusion restriction which have not been previously described.

There are no specific treatments against JC virus, and therapy has been based on anecdotal reports of efficacy or theoretical mechanisms of action that impair JC virus. Use of combination therapy with mirtazapine (which blocks 5-HT-2A receptor and JC virus entry) and mefloquine (which inhibits viral replication after viral entry) was described in a CVID patient with PML who also showed clinical improvement on this treatment [5]. However, a randomised trial assessing mefloquine failed to show benefit in reducing JC virus levels in the CSF, and no controlled trials for mirtazapine have been performed.

Infections are the most common neurological complications in CVID with a broad range including bacterial, fungal and viral pathogens. Whilst PML has been described, this is the first case of GCN in a patient with CVID. GCN should be considered in the differential diagnosis for immunodeficient patients presenting with isolated cerebellar syndromes.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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