SHORT REPORT

Reversible parkinsonism in a patient with progressive multifocal leucoencephalopathy

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A case of pathologically confirmed progressive multifocal leucoencephalopathy presenting with unilateral parkinsonism and cognitive decline that significantly improved over a 12-month period without any treatment is described. The patient had a background of chronic lymphocytic leukaemia, but had been in complete remission for 4 years at the time of diagnosis. This case is highly unusual not only in terms of the mode of clinical presentation in an apparently immunocompetent patient but also in that the patient spontaneously improved without any intervention. Progressive multifocal leucoencephalopathy should therefore be considered in the differential diagnosis of movement disorders developing in patients with a history of lymphoproliferative disease, even if they are in remission. Furthermore, such cases may not always require treatment, as the patient's immune system may overcome the viral disease process with spontaneous resolution of their neurological disorder.

A 39-year-old man presented with a 6-month history of stiffness and clumsiness affecting the right hand as well as mild but progressive difficulties with memory, concentration and word finding. The patient had been diagnosed with B-cell chronic lymphocytic leukaemia 11 years previously and had received treatment with chlorambucil, fludarabine, a course of CHOP (cyclophosphamide, vincristine, doxorubicin and prednisolone) and alemtuzumab (CamPath) before relapsing. He subsequently required two allogeneic bone marrow transplants (from the same donor) and a splenectomy, but had been in remission for 4 years at the time of presentation. During this 4-year period, he had received no immunosuppressive treatment, but had been dependent on red cell and platelet transfusion. At the time of presentation, he was no longer requiring transfusions, but was still receiving regular desferrioxamine for transfusion-related iron overload. He had not received cranial radiotherapy at any stage during his disease course.

Clinical examination showed hypomimia, micrographia and moderately severe bradykinesia and rigidity of the right upper limb. A diagnosis of idiopathic Parkinson's disease was suspected and he was started on cabergoline, 4 mg once daily, while imaging to exclude other pathology was awaited. Given the possibility of iron deposition in the basal ganglia as a possible contributory factor, venesection of 100 ml per week was also initiated. However, on review 3 weeks later, his right-sided parkinsonism had worsened and he had developed dyspraxia in his right hand as well as an expressive dysphasia. He scored 85/100 on the Addenbrooke's Cognitive Examination (mean (SD) normative score 93.8 (3.5))¹ at this stage. Formal neuropsychological testing showed moderate impairment in the domains of language (verbal fluency and semantic knowledge), verbal and non-verbal anterograde memory, and executive function

relative to his high predicted premorbid function. He was admitted for urgent investigation.

Blood tests showed a white cell count of $8.7 \times 10^9/l$ with a neutrophil count of $3.0 \times 10^9/l$ and lymphocyte count of $4.9 \times 10^9/l$, platelet count of $56 \times 10^9/l$, a haemoglobin level of 10.8 g/dl, a C-reactive protein level of 4 mg/l and an increased ferritin level of 3486 $\mu g/l$ (normal level 1–321 $\mu g/l$). Viral serology was negative for HIV and for human T lymphotropic virus types 1 and 2. The cerebrospinal fluid (CSF) was clear and acellular, with no organisms seen on gram and India ink stain and a negative cryptococcal antigen test; biochemical analysis showed a raised protein level of 0.81 g/l (normal 0.15–0.45 g/l), but normal CSF:serum glucose ratio (0.63). CSF polymerase chain reaction (PCR) was negative for Herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, enterovirus group and JC virus DNA. MRI of the brain (fig 1A) showed diffuse superior hemispheric white matter changes bilaterally but more extensively on the left, without mass effect, suggestive of progressive multifocal leucoencephalopathy (PML). There was no basal ganglia or brainstem involvement. A subsequent right frontal lobe biopsy showed patchy demyelination with bizarre enlarged astrocytes and abnormally large cells with a round nuclear outline, consistent with JC viral infection (see supplementary fig A1 online at <http://jnnp.bmjjournals.com/supplemental>). A number of blood vessels exhibited a prominent perivascular lymphocytic cuff (see supplementary fig A2 online at <http://jnnp.bmjjournals.com/supplemental>) that immunocytochemically included CD20 B-cells and CD3 T-cells. Subtyping showed both CD4 and CD8 T-cells, the latter comprising approximately 30% of the cells present (see supplementary fig A3 online at <http://jnnp.bmjjournals.com/supplemental>). Electron microscopy confirmed the presence of intranuclear viral inclusions, with appearances suggestive of polyoma virus infection (see supplementary fig B online at <http://jnnp.bmjjournals.com/supplemental>). DNA was extracted from the brain biopsy sample using standard techniques, and amplification of a target sequence within the viral protein 1 region of the JC virus genome using a nested PCR reaction proved positive. PCR products were separated on 2% agarose gel and visualised after ethidium bromide staining.

The patient had several seizures after the biopsy, which responded to carbamazepine. Treatment with the antiviral agent cidofovir was considered but not given, due in part to the lack of evidence to support its use in this context (see Discussion) and in part to the patient's clinical improvement, with spontaneous improvement in speech fluency and right upper limb dyspraxia being noted within 1 month from biopsy. At 1 year, his cognitive function had improved to normal: he scored 96/100 on the Addenbrooke's Cognitive Examination, and performance on computerised tests of frontal and temporal

Abbreviations: CSF, cerebrospinal fluid; PCR, polymerase chain reaction; PML, progressive multifocal leucoencephalopathy

Figure 1 Axial T2-weighted magnetic resonance images (A) at diagnosis, showing widespread high signal change in the superior hemispheric white matter, and (B) at 1 year showing significant resolution.

lobe function from the Cambridge Neuropsychological Automated Battery (CANTAB)² was within the normal range. The right upper limb dyspraxia was considerably improved, but there was mild residual rigidity and bradykinesia, unresponsive to a 2 week trial of co-beneldopa (250 mg daily). Neurological examination was otherwise normal. Further MRI of the brain at this stage showed a significant reduction in the extent of the cerebral white matter changes (fig 1B).

DISCUSSION

PML is a demyelinating disease of the central nervous system caused by JC virus, a member of the polyomavirus family of DNA viruses. The clinical spectrum of the disease varies with the distribution of demyelination, but typically includes visual impairment, sensory and motor deficits, gait abnormalities, speech and language disturbances, cognitive disorders and headaches.³ Although very rare, movement disorders including parkinsonism⁴ and isolated limb dystonia³ due to involvement of corticostriatal circuitry have been reported by previous authors. In our case, the principal clinical features of right-sided parkinsonism, dyspraxia and dysphasia were in keeping with the predominantly left frontoparietal distribution of pathology. The imaging does not suggest involvement of the basal ganglia, hence the parkinsonism is presumed to reflect disruption of thalamocortical or corticostriatal projections.

The diagnosis of PML was established beyond doubt in this case after brain biopsy, as the CSF PCR for JC viral DNA was negative. Although PCR has a specificity of 99%, its sensitivity is only 60–80%,⁵ hence brain biopsy with subsequent detection of JC viral protein or DNA remains the gold standard for diagnosis.

This case is unusual not only in terms of its initial clinical presentation with parkinsonism but also with respect to the clinical context in which JC infection arose. The infection is opportunistic, affecting immunocompromised individuals, and nowadays occurs most frequently in the context of HIV infection (constituting an AIDS-defining illness). However, the condition was first described in 1958 in individuals with lymphoproliferative disease,⁶ and before the emergence of HIV, chronic lymphocytic leukaemia was probably the most common disease association of PML. In such patients, however, PML is thought to almost always occur in the context of a low CD4 lymphocyte count and often in association with recent

treatment with the purine analogue fludarabine,^{7,8} neither of which apply to our patient, who had been in remission for 4 years. The history of allogeneic bone marrow transplantation in this patient may be relevant, although PML is very rare in bone marrow recipients,⁹ and the suppression of the immune response and resulting susceptibility to infection after bone marrow transplantation follow a predictable course and typically wanes after the first 12 months,¹⁰ so again, in our case, the development of PML is unusual as 8 years had elapsed after bone marrow transplantation. To our knowledge, only three similar cases of PML in apparently immunocompetent patients have been described in the literature.^{3,11,12} The mechanism of central nervous system infection in such individuals remains unclear, but it is possible that a qualitative rather than quantitative defect in CD4 lymphocytes allows reactivation of latent JC virus infection.

A further highly unusual feature of our case was the spontaneous recovery observed both clinically and radiologically. In the majority of cases, the natural history of PML is rapidly progressive neurological deterioration leading to death, usually within 6 months.^{5,6} In some organ transplant-associated cases, intervention to reverse immunosuppression has resulted in an improved outcome,⁵ whereas in HIV-associated cases, long-term survival without significant neurological improvement has been reported with highly active antiretroviral therapy.¹³ In those with underlying haematological disease, successful outcomes have been reported in individual cases after treatment with the antiviral agent cidofovir^{12,14} although, given that this agent does not significantly reduce JCV replication *in vitro*¹⁵ and that open-label trials in HIV-associated PML have failed to show clinical efficacy,^{16,17} these reports may in fact reflect spontaneous regression of PML. Further cases of functional recovery¹⁸ or stabilisation¹⁹ of the disease in haematological patients without intervention with antiviral agents have been described in the literature, although this is very rare. Such a favourable outcome may relate to an individual's ability to mount an effective T lymphocyte response to the JC virus. In a study of 26 patients with possible or proved PML, early detection of a specific JCV CD8 T cell response was associated with improved prognosis,²⁰ and in our case the presence of perivascular CD8 lymphocytic infiltrates in the brain biopsy suggests that such a response might have accounted for the rapid recovery observed.

In summary, we present a highly unusual case of PML causing an atypical parkinsonian syndrome in an apparently immunocompetent individual, but in the context of previous chronic lymphocytic leukaemia, in whom significant spontaneous improvement was observed both clinically and radiologically. We suggest that PML should be considered as part of the differential diagnosis of unusual neurological syndromes in patients with any lymphoproliferative disorder, even if in remission, and that such cases may not require active treatment as they can spontaneously resolve.

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Supplementary figures A1–A3 and B are available online at <http://jnnp.bmj.com/supplemental>.

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REFERENCES

- 1 **Mathuranath PS**, Nestor PJ, Berrios GE, *et al*. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology* 2000;**55**:1613–20.
- 2 **Sahakian BJ**, Owen AM. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. *J R Soc Med* 1992;**85**:399–402.
- 3 **Stockhammer G**, Poewe W, Wissel J, *et al*. Progressive multifocal leukoencephalopathy presenting with an isolated focal movement disorder. *Mov Disord* 2000;**15**:1006–9.
- 4 **Singer C**, Berger JR, Bowen BC, *et al*. Akinetic-rigid syndrome in a 13-year-old girl with HIV-related progressive multifocal leukoencephalopathy. *Mov Disord* 1993;**8**:113–16.
- 5 **Crowder CD**, Gyure KA, Drachenberg CB, *et al*. Successful outcome of progressive multifocal leukoencephalopathy in a renal transplant patient. *Am J Transplant* 2005;**5**:1151–8.
- 6 **Astrom KE**, Mancall EL, Richardson EP Jr. Progressive multifocal leukoencephalopathy; a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease. *Brain* 1958;**81**:93–111.
- 7 **Gonzalez H**, Bolger F, Camporo P, *et al*. Progressive multifocal leukoencephalitis (PML) in three patients treated with standard-dose fludarabine (FAMP). *Hematol Cell Ther* 1999;**41**:183–6.
- 8 **Cid J**, Revilla M, Cervera A, *et al*. Progressive multifocal leukoencephalopathy following oral fludarabine treatment of chronic lymphocytic leukemia. *Ann Hematol* 2000;**79**:392–5.
- 9 **Coley SC**, Jager HR, Szydlo RM, *et al*. CT and MRI manifestations of central nervous system infection following allogeneic bone marrow transplantation. *Clin Radiol* 1999;**54**:390–7.
- 10 **Wingard JR**. Advances in the management of infectious complications after bone marrow transplantation. *Bone Marrow Transplant* 1990;**6**:371–83.
- 11 **Bagnato F**, Pietropaolo V, Di Taranto C, *et al*. Chronic lymphocytic leukemia complicated by progressive multifocal leukoencephalopathy without apparent immunodepression. *Eur J Neurol* 2001;**8**:367–8.
- 12 **Aure K**, Behin A, Louillet F, *et al*. Dramatic improvement in non-AIDS related progressive multifocal leukoencephalopathy. *J Neurol Neurosurg Psychiatry* 2005;**76**:1305–6.
- 13 **Gasnault J**, Taoufik Y, Goujard C, *et al*. Prolonged survival without neurological improvement in patients with AIDS-related progressive multifocal leukoencephalopathy on potent combined antiretroviral therapy. *J Neurovirol* 1999;**5**:421–9.
- 14 **Viallard JF**, Lazaro E, Lafon ME, *et al*. Successful cidofovir therapy of progressive multifocal leukoencephalopathy preceding angioimmunoblastic T-cell lymphoma. *Leuk Lymphoma* 2005;**46**:1659–62.
- 15 **Hou J**, Major EO. The efficacy of nucleoside analogs against JC virus multiplication in a persistently infected human fetal brain cell line. *J Neurovirol* 1998;**4**:451–6.
- 16 **Gasnault J**, Kousignian P, Kahraman M, *et al*. Cidofovir in AIDS-associated progressive multifocal leukoencephalopathy: a monocenter observational study with clinical and JC virus load monitoring. *J Neurovirol* 2001;**7**:375–81.
- 17 **Marra CM**, Rajcic N, Barker DE, *et al*. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS* 2002;**16**:1791–7.
- 18 **Rueger MA**, Miletic H, Dorries K, *et al*. Long-term remission in progressive multifocal leukoencephalopathy caused by idiopathic CD4+ T lymphocytopenia: a case report. *Clin Infect Dis* 2006;**42**:e53–6.
- 19 **Price RW**, Nielsen S, Horten B, *et al*. Progressive multifocal leukoencephalopathy: a burnt-out case. *Ann Neurol* 1983;**13**:485–90.
- 20 **Du Pasquier RA**, Kuroda MJ, Zheng Y, *et al*. A prospective study demonstrates an association between JC virus-specific cytotoxic T lymphocytes and the early control of progressive multifocal leukoencephalopathy. *Brain* 2004;**127**(Pt 9):1970–8.