Progressive Multifocal Leukoencephalopathy in a Child with Hyperimmunoglobulin E Recurrent Infection Syndrome and Review of the Literature

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a fatal demyelinating disease due to infection with polyomavirus JC (JCV). PML occurs almost exclusively in immunocompromised patients, and although it has increased markedly in relation to AIDS, remains exceptional in children. We present the case of an immunocompromised child with hyperimmunoglobulin E recurrent infection syndrome (HIES) and pathologically-proven PML. HIES is a rare congenital immunodeficiency that to our knowledge has never before been reported in association with neurological complications. Following a recurrence of bronchopneumonia, the child's motor and cognitive functions deteriorated progressively in parallel with alterations on cerebral MRI. The neurological onset coincided with lymphocyte subset changes. PCR for JCV DNA did not detect the virus in CSF, and brain biopsy was required to secure the diagnosis. Antiviral treatment with cidofovir produced no benefit. Autopsy revealed the typical neuropathological findings of PML which were associated with inflammatory eosinophilic infiltrate (a marker of HIES). In accordance with the few pediatric PML cases reported and here reviewed, the child died five months after neurological onset.

Key words
Pediatric PML · Hyperimmunoglobulin E syndrome (HIES)

Introduction

Progressive multifocal leukoencephalopathy (PML) is a fatal progressive demyelinating disease that was first recognized by its unique histopathological pattern [2], and later shown to be associated with brain infection by the polyomavirus JC (JCV) [12, 26, 29]. PML was formerly rare, being reported sporadically in association with Hodgkin's disease [2], carcinoma, granulomatous inflammatory disorders such as tuberculosis and sarcoidosis, and immunodeficient states [8].

Since the beginning of the AIDS epidemic and the first description of AIDS-associated PML [27], the frequency of PML has increased markedly, resulting in improved case definition [4]. The established criteria for clinical diagnosis are focal signs and symptoms on neurological examination, focal white matter lesions on MRI or CT without mass effect, and exclusion of other causes of the clinical and neuroradiological findings. Pathological confirmation (on brain biopsy or autopsy specimens) requires demonstration of the triad demyelination, enlarged hyperchromatic oligodendrocyte nuclei, and enlarged astrocytes with bizarre hyperchromatic nuclei. When only two of these features are present, JCV is demonstrated by *in situ* hybridization or by electron microscopy. However, PML diagnosis is now facilitated by use of the polymerase chain reaction (PCR) to detect JCV DNA in cerebrospinal fluid (CSF), which may obviate the need for brain biopsy [14].

Despite the improvements in diagnosis, the prognosis for PML remains poor. Several drugs, including alpha-interferon, cytara-

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Table **1** Summary of published findings on pediatric PML associated with AIDS

Author, year	*Number of patients (sex, age)*	*How diagnosed*	*Therapy*	*Survival from diagnosis*
Brooks BR et al, 1984 [8]	1 (n. r.)	n. r.	n. r.	n. r.
Berger JR et al, 1987 [3]	16 (n. r.)	n. r.	n. r.	n. r.
Krasinki K et al, 1989 [24]	1 (n. r.)	n. r.	n. r.	n. r.
Dozic S et al, 1990 [17]	1 (M, 12 y)	Autopsy	Antibiotics	2 months
Holman RC et al, 1991 [21]	12 (n. r.)	n. r.	n. r.	4 – 5 months
Lang C et al, 1992 [25]	1 (M, 8 y)	n. r.	n. r.	n. r.
Vandersteenhoven JJ et al, 1992 [35]	1 (M, 7 y)	Brain biopsy	AZT	18 weeks
Singer C et al, 1993 [34]	1 (F, 13 y)	Brain biopsy	AZT + IFN α	10 months
Wrzolek MA et al,1995 [37]	1 (M, 12 y)	Autopsy	n. r.	few days
Araujo AP et al, 1977 [1]	1 (M, 10 y)	Brain biopsy	n. r.	n. r.
Morriss MC et al, 1997 [28]	1 (M, 7 y)	Brain biopsy	ddC	4 weeks
Berger JR et al, 1998 [5]	3 (5, 10, 13 y)	2 autopsy, 1 brain biopsy, 1 diagnosed clinically	n. r.	n. r.
Inui K et al, 1999 [22]	1 (M, 12 y)	PCR on CSF	AZT + ritonavir + lamivudine	n. r.

n. r.: not reported

Table **2** Summary of published findings on pediatric PML associated with inherited immunodeficiency syndrome

Author, year	*Sex/age of patient*	*Immunologic abnormalities*	*Diagnosis*	*Therapy*	*Survival*
Castaigne P et al, 1974 [11]	M/18 y	SCID, glioma	Autopsy	5-iodo-2 deoxyuridine	10 months
Walker DL 1978, [36]	F/5 y	SCID	Brain biopsy	n. r.	n. r.
Zu Rhein GM et al, 1978 [38]	M/11 y	SCID	Autopsy	n. r.	n. r.
Redfearn A et al, 1993 [32]	M/6 y	HIM	Brain biopsy	Cytosine arabinoside	9 months
Katz DA et al, 1994 [23]	M/15 y	Wiskott-Aldrich syndrome	Brain biopsy	Steroid	10 months
Bezrodnik L et al, 1998 [6]	M/5 y	Hypogammaglobulinemia	Brain biopsy	Cytosine arabinoside + IFNα	> 4 months

n. r.: not reported
SCID: Severe combined immunodeficiency; HIM: hyper IgM immunodeficiency.

bine, topotecan and, more recently, cidofovir [15] have been tried based on their ability to inhibit JCV *in vitro,* or reported efficacy in sporadic cases. However, none have been shown to be effective. In the only controlled trial published to date, cytarabine was used against PML in HIV-infected patients but provided no benefit [20].

As the number of cases increased, it became clear that PML rarely affects children. Most of the published pediatric cases have been associated with HIV (Table **1**), some with cell-mediated immunodeficiency due to transplantation, and a few with inherited immunological defects (Table **2**).

HIES is a rare immunodeficiency, first described by Buckley et al (1972) [9], and characterized by markedly elevated serum IgE (up to 100 times greater than normal) and recurrent staphylococcal abscesses in skin and lungs. Immune system investigations detect eosinophilia, variably defective granulocyte chemotaxis, but no clearly defined T-cell abnormalities [10]. Mucocutaneous candidiasis, coarse facial features, and other bone and teeth abnormalities are also described. Autosomal dominant transmission, but with variable expressivity, is suspected. The proximal 4q region seems to contain the disease locus [19].

We describe PML in an immunocompromised child with hyper-immunoglobulin E recurrent infection syndrome (HIES), the diagnosis of which was confirmed by brain biopsy and subsequent autopsy.

The interest in this particular case is not simply the rarity of PML in children, but its association with HIES – in which condition neurological complications have not previously been described.

Case Report

The patient, an eight-year-old boy, was the first-born child of a healthy father and a mother who died of synovial sarcoma at age 36. His five-year-old sister is in good health. The boy had suffered from recurrent skin infections since early childhood and had twice developed perineal cold abscesses. He had chronic pruritic eczematous dermatitis and chronic bronchopneumo-

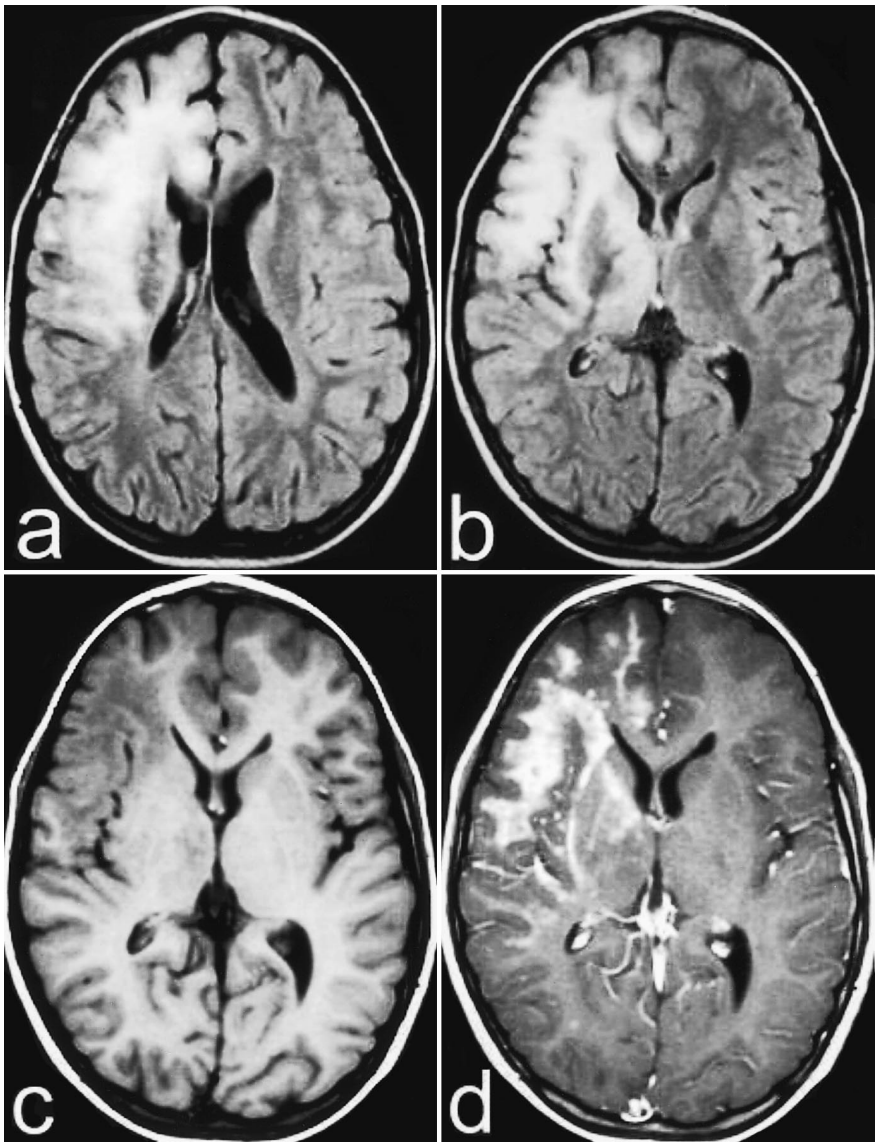

Fig. **1 a** to **d** **a and b** Axial MRI T_2-weighted, FLAIR TR 9999, TE 105, TI 180) showing extensive hyperintense lesions involving right frontal white matter, internal capsule and right thalamus. The gray matter is spared.
c and d Axial MRI (T_1-weighted, TR 600 TE 14, TR 560 TE 17). The lesions appear as hypointense areas. After gadolinium injection, strong enhancement is seen within the white matter. Interestingly, a dual enhancement pattern is present consisting of areas of diffuse enhancement interposed with multiple areas of punctate enhancement.

pathy, the latter related to a history of recurrent bronchitis and bacterial pneumonia. Periodic exacerbations of the lung condition – characterized by fever and productive cough with expectorant positive for *Staphylococcus aureus* or *Hemophilus influenzae* – had been treated with antibiotics. Prophylaxis for *Candida albicans* had also been given periodically. The hematological profile always showed normal neutrophils and lymphocytes, together with mild eosinophilia.

High levels of immunoglobulin E (1200 – 5400 UI/ml) were found repeatedly from an early age leading to a HIES diagnosis at age six. His *facies* were only slightly coarse. Normal platelet count and size excluded Wiskott Aldrich syndrome.

In June 1999, when he was 8 years 4 months old, following clinical worsening of his lung condition, the child underwent a lung CT which disclosed bronchiectasis involving the lingula, ventral portion of the superior lobe and medial lobe of the right lung, with associated interstitial inflammation. Enlarged lymph nodes were observed in various parts of the mediastinum. Blood tests showed high leukocyte (40,600 mm^3) and eosinophil (30,900 mm^3) counts. The expectorant was positive for *Hemophilus influenzae* and appropriate antibiotic treatment was initiated.

At the beginning of August of the same year, subtle emotional seclusion and cognitive slowness were reported by the family. At the same time, a mild weakness of the lower facial muscles on the left was observed. At the end of August, chest X-ray revealed the presence of a large new shadow in the paracardiac region of the right lung and diffuse interstitial involvement. The child was then admitted to the pediatric department. Clinical examination disclosed pale skin and mucosa, with eczematous lesions on the face and legs. Chest auscultation revealed widespread coarse rales and variable wheezing. Leukocyte count was 10,600 mm^3 (neutrophils 36.1%, lymphocytes 30.2%, monocytes 13.2%, eosinophils 20.5%), inflammatory indices were absent, but lymphocyte subsets were altered (CD3 29%, CD4 12%, CD8 15% and CD4/CD8 ratio 0.8: enhanced CD19 55%) whereas previously they had been normal. IgG was 1153 mg/dL, IgA 387 mg/dL, IgM 35 mg/dL, and IgE 2630 UI/dL.

At the beginning of September lymphocyte (1518 mg/dL) subsets had altered further (CD3 12%, CD4 4%, CD8 7%, CD19 71%, CD4/CD8 (0.6) as had the immunoglobulin profile (IgG 1412 mg/dL, IgA 168 mg/dL, IgM 19 mg/dL, and IgE 868 UI/dL). At this time, neurological evaluation showed hemiparesis including the face on the left limbs with brisk tendon reflexes and Babinski sign.

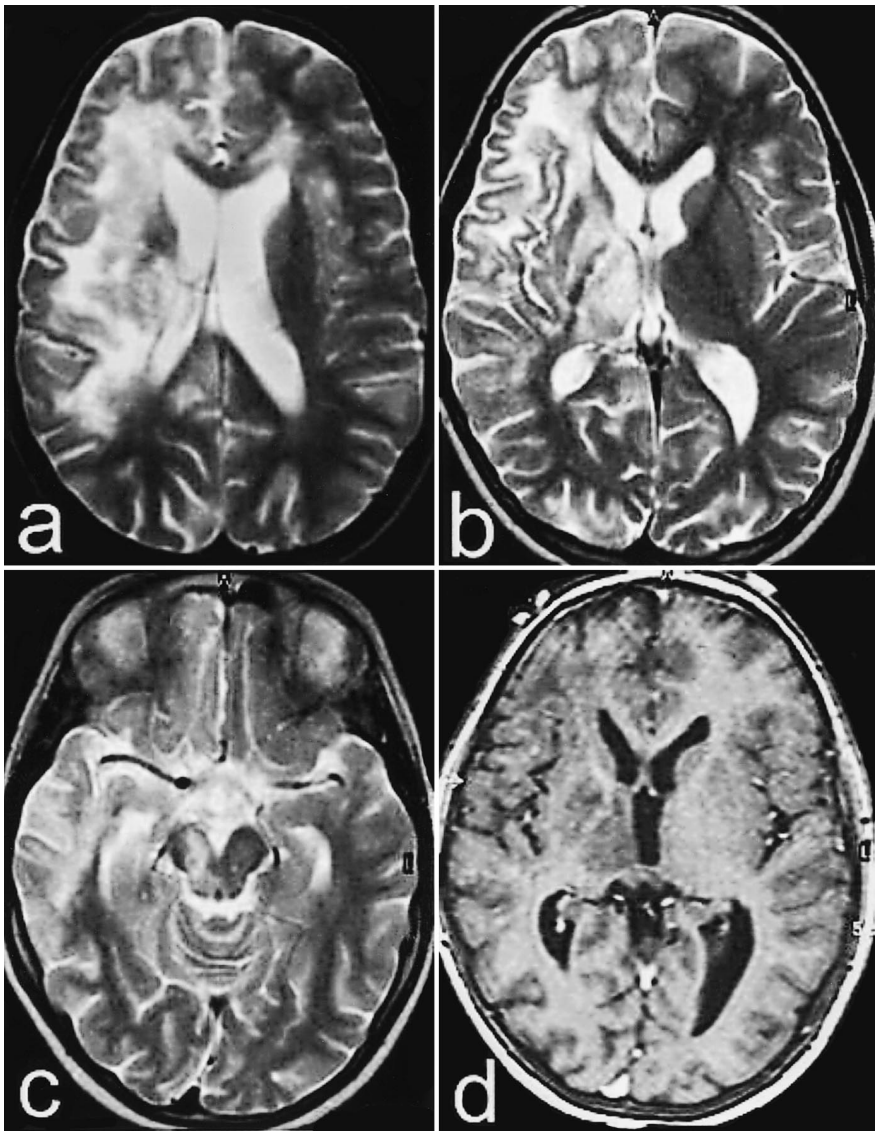

Fig. **2 a** to **d** **a to c** Axial T_2-weighted MRI (TR 2351, TE 90) obtained four weeks after those shown in Fig. **1**. Widespread involvement of the right frontal lobe and internal capsule, reaching the right cerebral peduncle, is evident. Mild hyperintensity is present within the left frontal lobe white matter, with initial involvement of the left genu of the corpus callosum. Both lateral ventricles and cerebral sulci are enlarged. **d** Enhanced axial MRI (T_1-FFE-weighted, TR 30, TE 4.6) shows conspicuous diffuse hypointensity; the enhancement previously present is no longer seen.

Quantitative testing of cognitive functioning was impossible because of the severe attentional deficit, slowness of thought and apathy. Cerebral MRI showed extensive hyperintense lesions (T_2-weighted images) in the right frontal white matter, internal capsule and right thalamus; the gray matter was spared. Gadolinium contrast showed strong white matter enhancement (Fig. **1**). Because of the neurological complications, the child was transferred to the neuropediatric department.

CSF analysis showed normal glucose, protein and cell counts; bacteria, mycobacteria, and fungi cultures were negative, as were PCR analyses for DNA of HIV, JCV, herpes simplex types 1 and 2, Epstein-Barr virus, varicella-zoster virus and cytomegalovirus.

A presumptive diagnosis of para-infectious encephalitis of unknown etiology was formulated, and twenty days after the onset of the neurological symptoms methylprednisone was initiated at 15 mg/kg/day, halving the dose every three days. There was no benefit, and within few days the spastic hemiparesis worsened, as did the apathy. Partial status epilepticus developed which was brought under control with intravenous phenytoin.

Cerebral MRI performed in mid-October showed hyperintensity involving the right frontal lobe and the internal capsule reaching the right cerebral peduncle; slight hyperintensity was also present in the left centrum ovale. No enhancement was observed on T_1 (Fig. **2**). At the same time, MRI-guided (Stealth Station, Sofamor-Danek) open brain biopsy was performed after parental consent and after delays due to the patient's neurological and respiratory condition which prevented general anesthesia. Neuropathological examination of the specimen revealed a few oligodendrocytes whose nuclei contained inclusions, several pleiomorphic astrocytes and lipid-laden macrophages. Electron microscopy demonstrated rare complete viral particles which seemed to be papovavirus. Immunohistochemistry with polyclonal whole anti-SV40 serum (Cytimmune anti-SV40 serum, Lee Biomolecular Research) revealed nuclear positivity in oligodendrocytes with and without nuclear inclusions. Hence PML was diagnosed. Subsequent PCR on a new CSF sample was positive for JCV.

Intravenous cidofovir (5 mg/kg with probenecid in saline infusion) was then initiated (two months after the onset of neurological symptoms), being given once a week for two weeks, then three further administrations at two weeks each. There was no

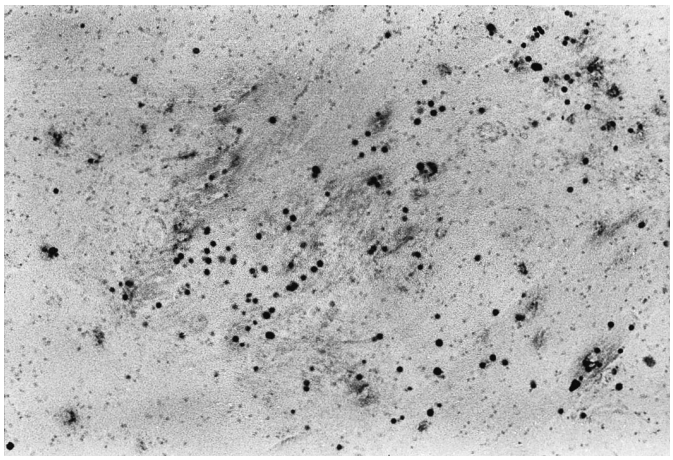

Fig. **3** Immunohistochemical demonstration of SV40 positivity in oligodendrocytes in a demyelinating lesion. Immunoperoxidase, hematoxylin counter-stain, × 200.

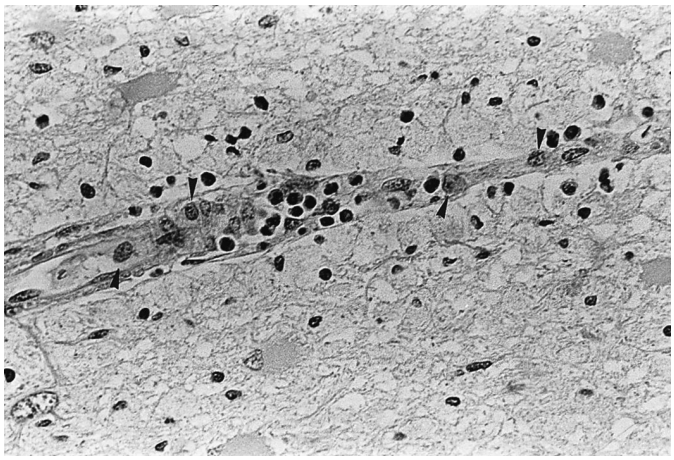

Fig. **4** Eosinophils in perivascular infiltrate in PML focus. Hematoxylin and eosin, × 400.

clinical benefit. A CSF sample obtained after the first two cidofovir infusions was still positive for JCV DNA.

In November, the child's condition deteriorated further, with development of severe spastic quadriparesis, supranuclear ophthalmoplegia and muteness. At the same time, the MRI alterations progressed to involve both hemispheres. Signs and symptoms of brainstem dysfunction then appeared and the child died five months after the neurological onset.

At autopsy, multiple focally confluent demyelinating lesions were present in both cerebral hemispheres, cerebellum, brainstem, and spinal cord. On microscopic examination all lesions were seen to be due to PML foci in various stages of evolution, from small subcortical lesions with few infected oligodendrocytes and minimal tissue damage, to huge demyelinating areas mainly composed of foamy macrophages. An inflammatory infiltrate rich in eosinophils was also observed, mainly perivascularly (Fig. **3**). Immunohistochemistry with anti-SV40 serum was positive for oligodendrocytes and, rarely, bizarre astrocytes (Fig. **4**).

Other major autopsy findings were bilateral bronchopneumonia, depletion of B-cell areas in lymph nodes and spleen, and rare nuclear inclusions positive for anti-SV 40 in renal tubule epithelial cells. Eosinophil-rich infiltrates were ubiquitously present in inflammatory foci in lungs and peripheral lymphoid tissue.

Discussion

Primary JCV infection usually occurs in a context of cellular immunodeficiency such as AIDS or immunosuppression. A few cases of PML have been described in association with a primary immunological defect not clearly due to cellular immunodeficiency [30,33]. Notwithstanding the complexity of the immunoregulation defect in HIES, it has been established that there is an alteration in cellular immunity. In most HIES patients, lymphocyte subsets are normal, as are *in vitro* lymphoproliferative responses to phytohemagglutinin (PHA), concanavalin A (conA), and pokeweed mitogens (PWM), whereas the response to *Candida albicans* antigens is usually low. Cytokine dysregulation, particularly deficient production of gamma IFN, may be responsible for the elevated IgE levels and the variable defect in neutrophil chemotaxis [7,16,31].

In our patient, the onset of neurological symptoms coincided with marked eosinophilia and lymphocyte subset changes – the latter suggesting cellular immunodeficiency. The neurological features were focal as in the common presentation of PML [18] although heralded by subtle mental changes. By contrast, seizures, which followed the appearance of the motor deficit, have been reported rarely in PML; they may have been related to the young age of our patient or to secondary cortical involvement.

The MRI findings were unusual both as regards lesion distribution and response to contrast. Although the main signal alterations were located frontally, as in the majority of patients [5], they also (and atypically) involved the basal ganglia and remained confined to one hemisphere for some time. The subcortical white matter lesions showed intense contrast enhancement. This feature is highly exceptional in PML, as shown for example in the large series, including children, reported by Berger et al [5]. The enhancement was likely related to severe blood-brain barrier disruption, as indicated also by the marked inflammatory features found on histopathological examination.

As is usual in PML, standard CSF analysis in our patient was unrevealing. The initial PCR investigation was also negative and this is consistent with the estimated 25 – 30% of false negative results for JCV in PML cases assayed at the onset of symptoms [13]. At this stage virus replication is probably still limited [13]. In spite of the negative PCR and atypical MRI findings, we suspected PML and this was confirmed by brain biopsy. The ensuing antiviral treatment (cidofovir) produced no clinical, radiological or virological improvement.

Numerous infections related to cellular immunodeficiency have been reported in children with HIES, including chronic mucocutaneous candidiasis, cryptococcosis, nocardiosis, aspergillosis, and even *Pneumocystis carinii* pneumonia; however, JCV infection has not previously been described in this setting.

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