

Successful Treatment of Cytomegalovirus Polyradiculopathy in a 9-year-old Child With Congenital Human Immunodeficiency Virus Infection

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Cytomegalovirus lumbosacral polyradiculopathy is a well-documented complication of human immunodeficiency virus in adults who have a CD4 count of less than 40/ μ L. Patients present with an acute ascending flaccid paralysis of the lower limbs with areflexia, paresthesia, and urinary and bowel symptoms. However, it appears to be rare in children with congenitally acquired immune deficiency

syndrome. We report a 9-year-old child with congenital human immunodeficiency virus infection who presented with cytomegalovirus polyradiculopathy and made an excellent response to cytomegalovirus treatment.

Keywords: human immunodeficiency virus; cytomegalovirus; polyradiculopathy

Cytomegalovirus lumbosacral polyradiculopathy in acquired immune deficiency syndrome (AIDS) is uncommon in children, and the response to treatment is uncertain. We report a child with cytomegalovirus polyradiculopathy who made an excellent neurological recovery following treatment.

Case Report

A 9-year-old African girl presented 2 weeks after arriving in the United Kingdom with weakness, inability to walk, and lumbar backache. She also had a cough, fever, hearing loss in the left ear, loose stools with central abdominal

pain, and weight loss. She was born to a human immunodeficiency virus (HIV)-positive mother, and was the second of 3 children of nonconsanguineous parents. She was exclusively breast-fed and had normal developmental milestones. About 6 months before presentation she had been treated for pulmonary tuberculosis. Details of the child's history including drug regimen were incomplete because she had been living with her grandmother for the preceding 4 years.

Examination findings included pallor, dehydration, malnutrition (weight < 0.4th centile), oral candidiasis, healed zoster scars in left thoracic 5/6 dermatomes, and finger clubbing. Respiratory and abdominal examinations were unremarkable. Neurological assessment revealed photophobia with no neck stiffness and right lower motor neuron facial weakness. She could sit unsupported but not walk independently. Tone was decreased globally. Power was 4/5 power in all limbs. Deep tendon reflexes were diminished at the ankles and knees, and plantar reflexes were flexor. Sensory examination was not possible due to the child's age and lack of cooperation (including language barrier). The lumbar area was not erythematous or tender. Over the next few days, she developed flaccid paralysis of the lower limbs and urinary retention requiring catheterization. Examination revealed significant reduction in power (Grade 0-2 in all muscle groups), with the left lower limb more affected than right, decreased tone, absent reflexes at the knees and ankles, and absent superficial abdominal reflex.

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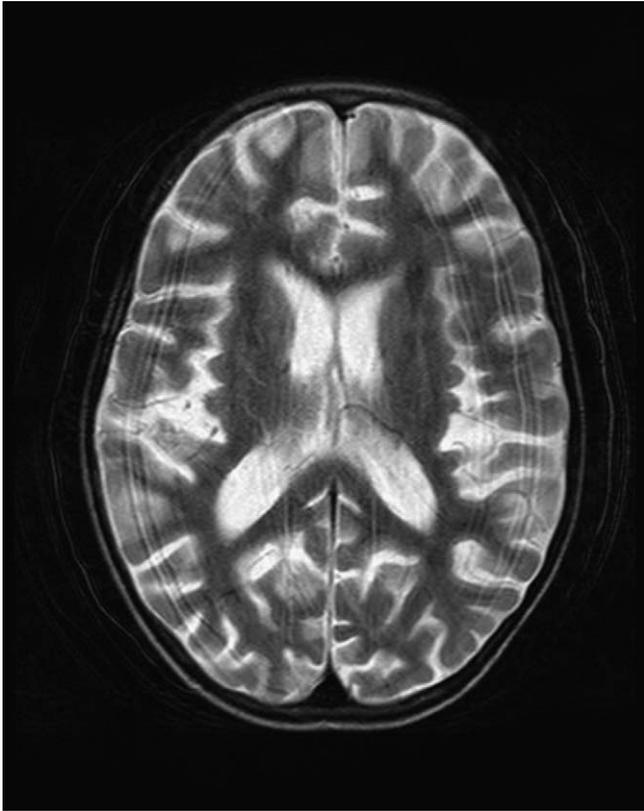


Figure 1. T2 axial magnetic resonance imaging (MRI) brain scan exhibiting generalized white matter loss and prominence of lateral ventricles.

Initial investigations revealed hyponatremic dehydration (sodium 147 mEq/L), anemia (hemoglobin 6.8 g/dL), mildly elevated inflammatory markers (C-reactive protein 33 mg/L), and a negative interferon gamma release assay for tuberculosis. Human immunodeficiency virus antibody was positive with a viral load of 206 200 copies/mL and the CD4 count was undetectable. Chest radiograph was consistent with bibasal infection but no signs of recent pulmonary tuberculosis infection. Lumbar puncture revealed turbid cerebrospinal fluid, white cell count 1502/ μ L (neutrophils 1380/ μ L, monocytes 18/ μ L, degenerative cells 104/ μ L), red blood cells 36 000/ μ L, glucose 0.8 g/L (blood glucose 4.7 g/L), protein 3.05 g/L, lactate 5.5 mmol/L, negative Gram stain, negative Zeil-Neilsen stain, and no growth after 5 days incubation. Magnetic resonance imaging (MRI) of brain revealed generalized white matter loss consistent with atrophy with slight prominence of ventricles (Figure 1).

She was commenced on antituberculosis therapy (isoniazid, rifampicin, ethambutol, and pyrazinamide) without corticosteroids. In addition, co-trimoxazole prophylaxis and fluconazole were started. The following differential diagnoses were considered: viral lumbosacral

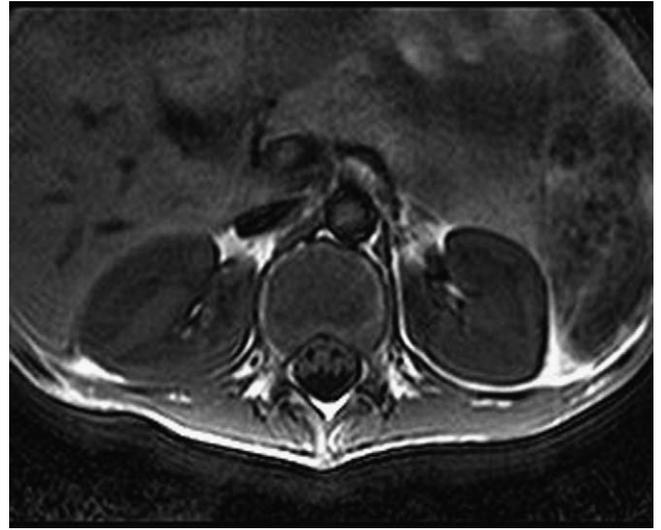


Figure 2. T1 axial magnetic resonance imaging (MRI) of spine with gadolinium enhancement revealing anterior displacement of cauda equina with enhancement of nerve roots.

polyradiculopathy, conus medullaris or cauda equina syndrome, polyneuropathy, and lymphomatous spinal mass.

Magnetic resonance imaging of spine revealed clumping and anterior displacement of the cauda equina with enhancement of the nerve roots consistent with arachnoiditis. There was further enhancement along the anterior and posterior aspect of the spinal cord following gadolinium (Figure 2). No signal abnormality was detected within the cord. Cerebrospinal fluid polymerase chain reaction (PCR) was positive for cytomegalovirus (12 226 000 copies/mL), and negative for varicella zoster, herpes simplex virus, Epstein-Barr virus, toxoplasma, and tuberculosis. Polymerase chain reaction for cytomegalovirus was also positive in the blood (1900 copies/mL). Neurophysiology studies revealed absence of F-waves in the lower limbs, which was consistent with a proximal conduction block to the lower limbs usually seen in arachnoiditis. An ophthalmology review revealed bilateral active cytomegalovirus retinitis.

A diagnosis of cytomegalovirus lumbosacral polyradiculopathy was made, and she was commenced on intravenous ganciclovir and foscarnet as well as highly active retroviral therapy. Her lower limb paralysis began to improve within 3 weeks of cytomegalovirus treatment and by 6 weeks she was able to walk without support. Bladder control improved and catheterization was stopped. A repeat ophthalmology review at 6 weeks revealed bilateral inactive cytomegalovirus retinitis. In view of this, and an excellent clinical response, ganciclovir was stopped after 10 weeks. Repeat cerebrospinal fluid analysis revealed normal parameters but PCR was still positive for cytomegalovirus (25 640 copies/mL). Within 2 weeks, the right

facial palsy returned; therefore, intravenous ganciclovir was restarted. Subsequent examination of cerebrospinal fluid continued to show normal values but persistence of cytomegalovirus, which remained sensitive to ganciclovir and foscarnet.

About 3 months after admission she developed pancytopenia. Bone marrow examination revealed abnormalities consistent with hemophagocytic lymphohistiocytosis. This did not improve with continued highly active retroviral therapy treatment. About 4 weeks prior to the onset of pancytopenia she had a repeat CD4 count, which was undetectable. She became increasingly unwell with general malaise and severe abdominal symptoms. Following discussion with her family, a palliative approach was taken and the child died 8 months after presentation.

Discussion

Cytomegalovirus infection is one of the most important opportunistic infections in the late stages of AIDS and can affect multiple organs.¹ The most common manifestation of neurological cytomegalovirus disease in HIV infection is retinitis followed by encephalitis, myelitis, multifocal polyneuropathy, and polyradiculopathy.²

Cytomegalovirus polyradiculopathy is well described in adults and can be the initial presentation of AIDS in approximately 13% of cases.³ It appears to be uncommon in children with AIDS. The reasons for this are unclear. To our knowledge, only 1 similar case has been reported in the French medical literature in a child.⁴ Human immunodeficiency virus–infected patients become susceptible to cytomegalovirus polyradiculopathy⁵ when the CD4 T-cell count is less than 40/ μ L. Cytomegalovirus polyradiculopathy typically affects the lumbosacral region and presents with ascending lower extremity weakness with diminished deep tendon reflexes that progress to areflexia.⁶ It may also present with paresthesia, urinary retention, and fecal incontinence. In AIDS, polyradiculopathy can also occur due to other etiologies, including toxoplasmosis, syphilis, lymphoma, tuberculosis, cryptococcus, Varicella-Zoster virus, Epstein-Barr virus, and Herpes-simplex virus.^{7,8}

Cerebrospinal fluid studies and spinal imaging are useful diagnostic aids in cytomegalovirus polyradiculopathy. Our patient had a mild, predominantly neutrophilic pleocytosis with an elevated protein and low glucose ratio that is typical of cytomegalovirus polyradiculopathy in the immunocompromised host. A review of 103 adult cases with cytomegalovirus polyradiculopathy³ exhibited mean values in cerebrospinal fluid white cell count of $651 \pm 1053/\mu$ L with an average of 68% neutrophils with protein 2.28 ± 1.78 g/L; cerebrospinal fluid/serum glucose ratio of 0.48 ± 0.17 g/L. This contrasts with the immunocompetent host, who exhibits a predominantly lymphocytic

response. Positive detection of cytomegalovirus in cerebrospinal fluid and blood with PCR aids to confirm the diagnosis.^{7,8} Our patient had the characteristic finding of far higher levels in the cerebrospinal fluid than blood. Cytomegalovirus can be cultured in up to 60% of cerebrospinal fluid samples.⁹ In cerebrospinal fluid samples, cytomegalovirus PCR has a sensitivity of 92% and specificity of 94%.³

Imaging can also be very useful in cytomegalovirus polyradiculopathy. Magnetic resonance imaging of the spine may show meningeal enhancement consistent with arachnoiditis and thickened nerve roots.¹⁰ There may also be evidence of root or cauda equina thickening. Magnetic resonance imaging is also useful to exclude cauda equina or spinal cord compressive lesions resulting from lymphoma, syphilis, or toxoplasmosis. Electrophysiology studies show wide spread denervation and prolonged or absent F-waves.¹ Our patient therefore had typical MRI spinal imaging and neurophysiology study findings.

Cytomegalovirus polyradiculopathy is universally fatal if untreated. Once diagnosed, treatment should be started promptly. Patients are usually commenced on ganciclovir, 5 mg/kg intravenously every 12 hours (induction therapy) for 10 to 14 days followed by 5 mg/kg intravenously per day, 5 days a week (maintenance therapy).⁹ If patient is already receiving treatment with ganciclovir or they are ganciclovir-resistant, then foscarnet can be added at 90 mg/kg intravenously once a day.¹¹ Ganciclovir can improve or stabilize over half the patients under treatment. In a case series of 56 adults with cytomegalovirus polyradiculopathy, 36% improved, 25% stabilized, and 39% continued to progress.³

Patients may show a dramatic response but a prolonged course of treatment may be necessary before any improvements are seen. Therefore, a prolonged or even indefinite course of treatment should be given if tolerated.¹¹ Some patients may exhibit viral drug resistance leading to treatment failure.¹² In this situation, a combination of ganciclovir and foscarnet may be more effective but this is associated with more side effects. Foscarnet may cause renal toxicity and ganciclovir causes bone marrow suppression; therefore, close monitoring of renal and bone marrow function is mandatory.

The long-term prognosis of cytomegalovirus polyradiculopathy in children is unknown. However, our patient had a dramatic and sustained improvement to treatment, which enabled her to discontinue urinary catheterization which she found very distressing. She also made a good functional recovery and was independently mobile within 6 weeks of treatment. Unfortunately, she developed hemophagocytic lymphohistiocytosis, which is a rare complication of many different infections including herpes viruses and is often fatal without bone marrow transplant.¹³ If she had not developed hemophagocytic lymphohistiocytosis, it is probable that she would have survived with an excellent

quality of life. Early recognition is likely to have improved her outcome and therefore cytomegalovirus polyradiculopathy should be considered in a child with human immunodeficiency syndrome who develops a new onset of lower limb weakness. Treatment courses can be long and difficult to administer but in our experience the potential benefits would outweigh these difficulties. We therefore recommend anticytomegalovirus treatment as soon as polyradiculopathy secondary to cytomegalovirus is strongly suspected or proven in children with AIDS.

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