HTLV-1 encephalitis

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Abstract

A 53-year-old woman with a background of human T-lymphotropic virus type 1 (HTLV-1) associated myelopathy presented with a subacute onset of upper limb weakness, sensory loss, and cerebellar dysfunction. Initial investigations demonstrated extensive T2 hyperintensity within the deep and subcortical white matter, with punctate contrast enhancement. CSF was lymphocytic with very high levels of HTLV-1 provirus in both CSF and peripheral blood lymphocytes. We diagnosed HTLV-1 encephalomyelitis and commenced high dose methylprednisolone followed by a slow steroid taper. The patient made a good recovery, and regained functional independence in the upper limbs.

Neurological manifestations of HTLV-1 infection extend beyond the classical tropical spastic paraparesis and are under-recognised. We review the literature on HTLV-1 encephalitis, and discuss its diagnosis and management.

Case presentation

A 53-year-old woman of Black British ethnicity, diagnosed with HTLV-1-associated myelopathy seven years previously, presented with a three-week history of upper limb weakness and sensory change, head tremor, diplopia, and ataxia. There was no change in her longstanding spastic paraparesis, from which she had become bedbound within two years of her initial presentation. Following the development of sacral osteomyelitis, methotrexate, taken for HTLV-1-associated myelopathy, had been stopped three months previously.

Examination revealed an alert and orientated patient with a 'no-no' head tremor and prominent multi-directional nystagmus. In the upper limbs there was increased tone, pyramidal weakness, dysmetria, intention tremor, brisk reflexes, and distal sensory change bilaterally. Observations and initial laboratory investigations were unremarkable.

An MRI brain scan demonstrated extensive patchy T2 hyperintensity within the deep and subcortical white matter, brainstem, and cervical cord, with multifocal punctate enhancement in both hemispheres, and pial enhancement over the spinal cord, 5th, 7th and 8th cranial nerves (**Figure 1**).

Cerebrospinal fluid (CSF) examination demonstrated a lymphocytic pleocytosis (white cell count 35, lymphocytes 84%, mononuclear cells 16%), raised protein (1.5 g/L) and low relative glucose (2.9 mmol/L, serum 6.5 mmol/L). HTLV-1 proviral load was 36% (36 HTLV-1 DNA copies per 100 cells) in peripheral blood mononuclear cells (PBMC) and 72% in CSF. CSF neopterin was 308 pmol/ml and chemokine (C-X-C motif) ligand 10 (CXCL10) 5095 pg/ml, measured by ELISA, were both well above cut-offs of 44 and 4400, respectively, associated with rapid progression of HTLV-1-associated myelopathy.¹ Neurofilament light chain was markedly raised (4249 pg/ml, age corrected normal <890).²

We diagnosed HTLV-1 encephalitis. The patient was managed with 1 gram of intravenous methylprednisolone daily for three days followed by 1mg/kg oral prednisolone, prior to recommencing weekly oral methotrexate with folic acid cover. Within one month the diplopia, tremor, and ataxia resolved and she regained functional independence in the upper limbs.

Discussion

Endemic to Japan, sub-Saharan Africa, Central and South America, and the Caribbean, an estimated 10-million people are infected with HTLV-1 worldwide (**Figure 2**).^{3, 4} The vast majority of those infected remain asymptomatic throughout their lives. 5% will develop adult T-cell leukaemia/lymphoma, while in 3% there is a relentlessly progressive spastic paraparesis, termed tropical spastic paraparesis prior to the discovery of its viral aetiology and reclassification as HTLV-1-associated myelopathy.^{5, 6}

HTLV-1-associated myelopathy typically presents as an insidious and slowly progressive spastic paraparesis, resulting in wheelchair dependence after a median 21 years.⁷ Pathologically characterised by perivascular lymphocytic infiltrates with a predilection for the thoracic spinal cord, axonal loss occurs secondary to neuronal exposure to the inflammatory milieu.^{5, 8}

HTLV-1 proviral load is the strongest predictor for the development of HTLV-1-associated myelopathy, which is rare if the proviral load is less than 1%. After an initial acute phase the proviral load for each individual remains relatively stable over time, while varying >100,000 fold between individuals.¹

The host T-cell response, governed by the host genotype, is the principal determinant of risk in HTLV-1 infected patients. Human leukocyte antigen genotype, forkhead box protein P3 frequency, and a number of single nucleotide polymorphisms play a role in determining both the proviral load and the inflammatory response to the virus.⁵

HTLV-1 encephalitis is a rarely reported entity, yet of ten cases so far described worldwide this is the fourth case from the United Kingdom.⁶ As with other encephalitides, patients present with alterations of consciousness, fevers, headaches, focal neurological deficits, or seizures. While most patients have myelopathy prior to the onset of encephalitis, cases of HTLV-1 encephalitis are reported in those without myelopathy.^{9, 10} All but one of the ten reported cases are female.

Diagnosis is guided by CSF and imaging findings. Typically, CSF demonstrates a lymphocytic pleocytosis, however it is the HTLV-1 proviral load which identifies HTLV-1 as the cause. We know from the HTLV-1-associated myelopathy literature that the risk of myelopathy rises exponentially when the HTLV-1 proviral load surpasses 1%, while a high

HTLV-1 proviral load in the CSF compared to PBMCs (CSF:PBMC HTLV-1 proviral load ratio) demonstrates selective infiltration of HTLV-1 into the CNS. Those with a CSF:PBMC HTLV-1 proviral load ratio <1 remain asymptomatic, while those with HTLV-1-associated myelopathy invariably have a CSF:PBMC HTLV-1 proviral load ratio >1 .^{11, 12} Levels of the cytokines CXCL10 and neopterin within the CSF are both strongly correlated with the rate of disease progression in HTLV-1-associated myelopathy, while neurofilament light chain levels demonstrate acute neuronal damage.^{1, 13} CXCL10, produced by astrocytes in response to interferon-gamma secreted by HTLV-1-infected T cells, promotes migration of infected T cells into the CNS; a positive feedback loop that results in chronic inflammation.^{5, 14} MRI brain imaging typically demonstrates patchy or confluent T2 hyperintensities in the subcortical white matter and brainstem.⁶

This patient's imaging findings (**Figure 1**), their existing diagnosis of HTLV-1-associated myelopathy, and the high CSF:PBMC HTLV-1 proviral load ratio and cytokine levels indicated HTLV-1 as the cause of their presentation. HTLV-1 associated inflammation had extended beyond the thoracic spinal cord to cause an HTLV-1 encephalitis. The high CSF cytokine and neurofilament light chain concentrations reflect the degree of inflammation and neuronal damage. While the majority of patients with HTLV-1 infection remain asymptomatic, this patient was wheelchair dependent within two years of their first symptoms, fulfilling the criteria for rapidly progressive HTLV-1-associated myelopathy. Despite being wheelchair dependent, immunomodulation with methotrexate had previously been maintained to protect upper limb function. Cessation of methotrexate likely triggered the new deterioration.

Antiviral agents are ineffective in established HTLV-1 infection where cell proliferation, as opposed to viral spread, maintains proviral load.¹⁵ While the mainstay of management for HTLV-1-associated myelopathy is symptomatic management of the spastic paraparesis, bowel, and bladder symptoms, immunosuppression can slow progression and is of particular value in those with extraspinal neurological manifestations, although evidence for efficacy remains limited.^{5, 15} Current consensus guidelines for the management of HTLV-1-associated myelopathy advise pulsed methylprednisolone in those with progressive disease, followed by consideration of maintenance oral steroids. HTLV-1

encephalitis is generally managed similarly, as a severe manifestation of the same disease process.¹⁶ Steroids slow motor deterioration, while a number of agents including ciclosporin, azathioprine, and methotrexate have a role where steroids are ineffective or poorly tolerated.^{5, 15}

It is important in these patients to exclude other potential aetiologies for their encephalitic presentation. HTLV-1 modulates the immune response resulting in a subclinical immunosuppressed state,^{17, 18} while any coincidental or causative infective process can be exacerbated by immunosuppression given to treat HTLV-1 related inflammation. Routine screening in these patients should include HIV, hepatitis B and C, syphilis, and tuberculosis alongside testing of CSF for common central nervous system viral and bacterial infections, and *Strongyloides stercoralis* and schistosomiasis where there is any history of travel to an endemic region.¹⁶

There is increasing evidence that the pathological process of HTLV-1 infection extends beyond the thoracic cord. Infiltrates within the muscle, nerves, and brain result in myopathy, neuropathy, and encephalitis; predominantly but not exclusively in those with myelopathy.⁸ Prompt identification and management, including increased immune suppression can result in favourable clinical outcomes.

Box 1

Key points:

- Consider HTLV-1 encephalitis in all patients with known or suspected HTLV-1 infection presenting with symptoms consistent with encephalitis.
- Typical CSF findings in HTLV-1 encephalitis include an HTLV-1 proviral load >1% (DNA copies per 100 lymphocytes) and CSF:PBMC HTLV-1 proviral load ratio >1. MRI imaging demonstrates MRI T2 hyperintensities within the brainstem and subcortical white matter.
- HTLV-1 encephalitis can have good outcomes when managed promptly with immunosuppression, typically high dose steroids initially.

- Infective causes and intercurrent infections must be excluded before commencing immunosuppressive treatment (including HIV, hepatitis B and C, syphilis, and tuberculosis).
- A dedicated HTLV team, based at The National Centre for Human Retrovirology, Imperial College Healthcare NHS Trust, can provide advice in situations of diagnostic uncertainty (Imperial.htlv@nhs.net).

Further reading

Cranshaw et al., Human T-cell lymphotropic virus (HTLV)-associated encephalopathy: an under-recognised cause of acute encephalitis? Case series and literature review. *J Neurol* . 2018 Apr;265(4):871-879

Araujo et al. Management of HAM/TSP Systematic review and consensus-based recommendations 2019. *Neurol Clin Pract*. 2020 Mar; 10.1212.

Competing interests

The authors report no competing interests.

Figure legend

Figure 1: MRI brain imaging in HTLV-1 encephalitis

MRI brain imaging demonstrated patchy T2/flair hyperintensity in the deep and subcortical white matter of both hemispheres involving the midbrain and superior cerebellar peduncles (**A**). The larger lesions demonstrated intermediate diffusivity (**B**). Following contrast there was leptomeningeal (arrow) and trigeminal nerve enhancement (arrowheads, **C**) alongside multifocal punctate enhancement in both cerebral hemispheres (**D**).

Figure 2: Map demonstrating HTLV-1 prevalence

The main endemic areas of HTLV-1 infection are south-western Japan and parts of the Caribbean and its surrounding regions. The infection is also endemic to parts of South America, intertropical Africa and in the Middle East (particularly the Mashhad region in Iran). Romania is the only endemic HTLV-1 region in Europe. Map created using the European Centre for Disease Prevention and Control (ECDC) Map Maker tool. The classification for high and low prevalence is in accordance with the ECDC report on the geographical distribution of areas with a high prevalence of HTLV-1 infection, with a cut-off of over 1/10,000 among first time blood donors and/or 1% in the adult population.⁴

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