# Pontocerebellar inflammation and pancytopenia

**Authors:**

Alex Dudley[1], Derville O'Shea[2], Noel Fanning[3], Niamh Bermingham[4], Brian Sweeney[1], Simon Cronin[1,5]

**Author Affiliations:**

[1]Department of Neurology, Cork University Hospital, Cork, Ireland

[2]Department of Haematology, Cork University Hospital, Cork, Ireland

[3]Department of Radiology, Cork University Hospital, Cork, Ireland

[4]Department of Neuropathology, Cork University Hospital, Cork, Ireland

[5]School of Medicine, College of Health and Medicine, University College Cork, Cork, Ireland

**Corresponding author:**

Professor Simon Cronin, Department of Neurology, Cork University Hospital, Cork

simon.cronin@hse.ie

**Word Count: 1,475**

**Case Presentation**

A 19-year-old woman had a one-week history of gradual onset headache, vomiting, double vision and unsteadiness. She had been previously well.. She had no sick contacts and her last foreign travel had been to Nepal over 5 years before. She was febrile at 38.4 °C but systemic examination was otherwise normal. She had an ataxic gait, left 6$^{th}$ and 7$^{th}$ cranial nerve palsies, brisk lower limb reflexes and right ankle clonus.

CSF showed lymphocytic pleocytosis with 24 cells/μL (≤5), protein was raised at 1.01 g/L (0.15–0.45), and glucose was 3.0 mmol/L (plasma 5.1). Viral and bacterial tests including TB stains and culture were negative. There were no oligoclonal bands. Routine bloods, inflammatory markers, infective serology, vasculitis screen and serum-angiotensin converting enzyme (ACE) were normal.

MR scan of brain showed extensive leptomeningeal enhancement, as well as patchy white matter signal abnormality and enhancement mainly affecting the pons and cerebellum, but also in the right frontal lobe (FIGURE 1). MR scan of spine showed a short segment of right sided T2/STIR high signal and patchy enhancement in the thoracic cord.

**What is the most likely differential diagnosis?**

The radiological differential diagnoses included acute demyelinating encephalomyelitis (ADEM) and sarcoidosis. However, the posterior fossa abnormalities resembled chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). Given the subacute onset over days and fever, we first considered an infective rhombencephalitis, including bacterial causes such as tuberculosis, listeria and Lyme disease; viral causes such as herpes simplex virus 1 and 2, SARS-CoV2, Epstein–Barr virus and cytomegalovirus. Other differentials included sarcoidosis, Bickerstaff's encephalitis, ADEM, Behçet's syndrome and myelin oligodendrocyte glycoprotein (MOG)-associated disease. CLIPPERS is usually not associated with meningeal or spinal cord involvement. Toxins, neoplastic, paraneoplastic and autoimmune encephalitis seemed less likely.

Quantiferon, MOG, aquaporin-4, GFAP, ganglioside and paraneoplastic antibodies were negative. Repeat CSF again showed a mild lymphocytic pleocytosis, with negative cultures and viral PCR, benign cytology, but with slightly elevated CSF ACE at 1.47 μmol/min/L (0–1.2). CT scans of thorax, abdomen and pelvis showed a few small non-specific pulmonary nodules only. Positron-emission tomography scan showed no evidence of malignancy.

There was little early improvement despite starting broad-spectrum antibiotics and antivirals. However, her neurological symptoms significantly improved after adding corticosteroids with a slow oral taper. Over the next three months, she had two ataxic relapses but the symptoms and brain imaging seemed to respond very well to corticosteroids and plasma exchange. She was started on rituximab and made a very good neurological recovery.

One year later, she re-presented with new cranial neuropathies, new ataxia requiring assistance to walk, fever, myalgias and epigastric pain. Transiently, her peripheral lymphocyte count was 0.23 x $10^9$/L (0.9–3.2), platelets 80 x $10^9$/L (140–440) with a moderate transaminitis. Infective screen and hepatitis serology were unremarkable. Serum ACE was again normal. MR scan of brain showed new T2 hyperintensities and enhancement (FIGURE 2). Repeat CT of thorax showed a cavitating 9 mm right upper lobe nodule, and a single small granuloma in the liver. CSF ACE was again raised at 1.86 μmol/min/L. Cytology was benign, cultures were negative, and JC virus DNA was not detected.

**What is the most appropriate next step?**

We sought tissue samples. Lung biopsy was consistent with an obstructive pneumonia with foamy macrophages and inflammatory infiltrate, with a tiny focus of eosinophilic necrosis but no granulomas. Cerebellar biopsy showed a meningoencephalitis, with leptomeningeal lymphocytic inflammation and parenchymal perivascular lymphohistiocytic aggregates with small non-necrotising granulomas (FIGURE 3). Cerebellar TB stains and culture were negative.

She regained independence on re-treatment with high dose corticosteroids. The working diagnosis was neurosarcoidosis and she was treated with infliximab, methotrexate and tapering oral corticosteroids. Over the next year her neurological symptoms remained stable and MR brain scan

showed cerebellar atrophy but no new inflammation. She was hospitalised for several infections including SARS-CoV2 and disseminated cutaneous varicella zoster virus.

Eighteen months after the brain biopsy, she again presented systemically unwell, with fever, transaminitis and new upper limb subcutaneous nodules. She was covered with broad-spectrum antibiotics and antifungals. She developed pancytopenia, and a subcutaneous nodule biopsy identified a primary cutaneous gamma-delta T-cell lymphoma. Bone marrow biopsy confirmed haemophagocytic lymphohistiocytosis (HLH). She had low fibrinogen and markedly elevated triglycerides (five times upper limit of normal) and ferritin (seven times upper limit normal). We gave high-dose corticosteroids and ciclosporin, and subsequently started CHEOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone).

Shortly after the first cycle of chemotherapy she presented with neutropenic sepsis and recurrence of diplopia, but her neurological and cognitive examinations were otherwise stable. MR scan of brain at two months since last imaging showed a new, different pattern of widespread T2/FLAIR hyperintensity, without enhancement, through much of the brainstem and periventricular cerebral hemispheres (FIGURE 4).

**What is the differential diagnosis for the new MRI appearance?**

A possible toxic reaction to chemotherapy was considered most likely. The confluent nature of the T2/FLAIR abnormalities also raised suspicion for progressive multifocal leukoencephalopathy. Initial CSF testing appeared to confirm the presence of JC virus DNA. However, she did not develop any neurological signs related to the diffuse T2/FLAIR abnormalities, which improved markedly back to baseline on interval imaging a month later, all making progressive multifocal leukoencephalopathy unlikely. Repeat CSF showed a decrease in JC virus DNA from 27,474 IU/mL to <100 IU/mL.

Based on recent literature reporting the co-occurrence of HLH and a CLIPPERS-like neuroinflammation[1], we sent a genetic panel for familial HLH. This identified a previously reported homozygous variant in the *RAB27A* gene (c.136T>A; p.Phe46Ile) consistent with Griscelli syndrome type 2 (familial HLH). She had already been referred for haematopoietic stem cell transplantation

(HSCT) for gamma delta T-cell lymphoma, but unfortunately developed severe non-neurological complications of systemic HLH and passed away.

**Discussion**

Haemophagocytic lymphohistiocytosis is a life-threatening syndrome of excessive immune activation that can mimic sepsis. It can be primary or secondary. The primary form is genetic and autosomal recessive. It typically presents in infancy or early childhood with systemic symptoms. Abnormalities in perforin-dependant cytotoxicity are most common, and result in unrestricted macrophage and lymphocytic activation with multiorgan involvement. The secondary form results from immunological triggers such as malignancy or infection. The HLH 2004 diagnostic criteria require 5 of 8 criteria including fever, splenomegaly, cytopenias, hypertriglyceridaemia or hypofibrinogenaemia, evidence of haemophagocytosis (in bone marrow, spleen or lymph nodes), low or absent NK cell activity, hyperferritinaemia and elevated sIL-2r. [2] A genetic diagnosis does not require the same level of clinical evidence. This patient at first presentation had fever, but normal blood counts, ferritin and immunoglobulins. It was over a year before she developed transient cytopenias and 30 months to developing HLH.

Neuroinflammatory disease can be an isolated manifestation of primary HLH. It is rare but likely under-recognised. Diffuse multifocal white matter changes with a predilection for the cerebellum is most common, while leptomeningeal enhancement occurs in fewer than 20 percent. Brain biopsies most commonly show a T-cell predominate lymphohistiocytic infiltration, occasionally showing necrosis and granulomas. [3]

Adult-onset primary HLH with isolated CNS manifestations is very rare. A literature review in 2021 identified eight cases [4], though there have since been more reports. A genetic study of twelve patients with CLIPPERS identified primary HLH biallelic variants in a third of them; none met criteria for systemic HLH. [1]

HLH-directed therapy, such as the HLH 2004 treatment protocol followed by HSCT can improve survival and outcomes in systemic HLH. It is less clear if HSCT or immunotherapies such as alemtuzumab are best to treat isolated CNS disease. [2,3]

In people with systemic HLH, the likelihood of identifying a genetic cause decreases with age. Widespread genetic testing of adults with systemic HLH is not recommended, especially if there is a recognised immunologic trigger such as lymphoma. Our reason for testing this patient was that we suspected a unifying diagnosis to explain the CLIPPERS-like neuroinflammatory syndrome.

Genetic causes of HLH can be divided into familial HLH and familial HLH-related disorders. Familial HLH encodes proteins important for the cytotoxic granule formation and release pathway, such as perforin. Familial HLH-related disorders, including Griscelli syndrome type 2, have variants that cause a congenital immunodeficiency syndromes with an increased incidence of HLH. [5]

Griscelli syndrome type 2 is caused by variants in *RAB27A*, which is important in secretory vesicle trafficking and exocytosis. [5] It typically presents in infants, and may be clinically suspected due to reduced melanocyte activity or albinism, but there have been reported cases without hypopigmentation like the case we report here [6]. *RAB27A* variants result in immunodeficiency, known to increase the risk of infections and of malignancies, including lymphoma. Neurological involvement may be the presenting feature, with waxing and waning multifocal encephalomyelopathy. *RAB27A* is not expressed in neuronal cells, CNS involvement is probably due to lymphohistiocytic inflammation. Treatment with corticosteroids may mask the systemic features of HLH [7].

We are not sure why this patient transiently had JC virus DNA detectable in her CSF, but it was probably an artefact as it did not correlate with the radiological course. *RAB27A* knockdown in vitro can protect against infective spread of JC virus through neuronal cultures, but it is unknown if this is clinically relevant [8].

Our interpretation is that this patient had adult-onset primary HLH owing to *RAB27A* mutation, presenting initially with isolated CNS inflammation then followed by recurrent episodes of fever,

infection and cytopenia. There are several reports of separate emergence of lymphoma in people with *RAB27A* variants, because of attenuated malignancy immunosurveillance [9].

The clinical presentation, imaging and biopsies are often non-specific in isolated CNS HLH. Clinicians require an increased awareness of this disease entity, and a very high index of suspicion to detect it before systemic, life-threatening HLH develops. Early detection allows genetic testing of siblings and appropriate treatment.

**Key points**

- Adult-onset genetic forms of haemophagocytic lymphohistiocytosis (HLH) can present with a non-specific isolated CNS neuroinflammatory syndrome
- Familial HLH can masquerade as neurosarcoidosis (overlapping histological features) or CLIPPERS (overlapping radiological features)
- Clinicians need a high index of suspicion to diagnose this rare but treatable condition, including appropriate genetic testing and treatment of siblings

**Further Reading**

Taieb G, Kaphan E, Duflos C, *et al*. Hemophagocytic Lymphohistiocytosis Gene Mutations in Adult Patients Presenting With CLIPPERS-Like Syndrome. *Neurol Neuroimmunol Neuroinflamm* 2021:8(e).

Blincoe A, Heeg M, Campbell PK, *et al.* Neuroinflammatory Disease as an Isolated Manifestation of Hemophagocytic Lymphohistiocytosis. *J Clin Immunol* 2020; 40: 901-16.

**References**

1. Taieb G, Kaphan E, Duflos C, *et al*. Hemophagocytic Lymphohistiocytosis Gene Mutations in Adult Patients Presenting With CLIPPERS-Like Syndrome. *Neurol Neuroimmunol Neuroinflamm* 2021:8(e).

2. Henter JI, Horne A, Arico M *et al.* HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;48:124-31.

3. Blincoe A, Heeg M, Campbell PK, *et al.* Neuroinflammatory Disease as an Isolated Manifestation of Hemophagocytic Lymphohistiocytosis. *J Clin Immunol* 2020; 40: 901-16.

4. Southam C, Grossman J, Hahn C. Primary Adult-Onset Hemophagocytic Lymphohistiocytosis with Neurologic Presentation. *Can J Neurol Sci* 2022; 49:441-4.

5. Lindahl H, Bryceson YT. Neuroinflammation Associated With Inborn Errors of Immunity. *Front Immunol* 2021;12:827815.

6. Ohishi Y, Ammann S, Ziaee V, *et al.* Griscelli Syndrome Type 2 Sine Albinism: Unraveling Differential RAB27A Effector Engagement. *Front Immunol* 2020;11:612977.

7. Alessandra T, Gianluca M, Alessandra E *et al*. Griscelli syndrome type 2: A well defined diagnosis with an intriguing diagnostic way. *Neuroimmunology Reports* 2022;2:100091.

8. Morris-Love J, O'Hara BA, Gee GV *et al.* Biogenesis of JC polyomavirus associated extracellular vesicles. *J Extracell Biol* 2022;1:e43.

9. Blanchard G, Atallah I, Blanchard M. Primary cutaneous T-cell lymphoma not otherwise specified (NOS) uncovering a novel RAB27A variant in Griscelli syndrome type 2. *Br J Dermatology* 2024;ljae412

**Figure Legends**

**Figure 1**

MR scan of brain at initial presentation showing (A) punctate FLAIR hyperintensities in the pons and cerebellum *arrows*, (B, C) axial and coronal post-contast T1 with small (<3 mm) punctate and curvilinear pontine enhancements and diffuse leptomeningeal enhancement along the cerebellar folia *arrowheads* and (D) right frontal perenchymal FLAIR hyperintensity

**Figure 2**

MR scan of brain at one year, showing (A) new and larger T2 hyperintensities predominantly affecting the pons and cerebellum. (B, C) Post-contrast T1 weighted imaging showing larger parenchymal enhancements and extensive leptomeningeal enhancement.

**Figure 3**

Cerebellar biopsy one year after initial presentation showing (A) white matter non-necrotising granuloma and encephalitis and (B) leptomeningeal T-lymphocytic inflammation

**Figure 4**

MR scan of brain three years after initial presentation showing (A, B) widespread new FLAIR hyperintensities affecting the midbrain and bilateral paratrigonal white matter. (C, D) There is significant radiological improvement two months later.

**Contributors**

AD, DOS, BS and SC were involved in patient management, drafting and editing of manuscript. NF and NB were involved in clinical investigations, data interpretation, figure creation and revision of manuscript. SC is the guarantor.

**Funding**

None declared

**Competing interests**

None declared

**Patient consent for publication**

Written Consent obtained from patient's family

**Ethics approval**

Not applicable

**Acknowledgements**

Not applicable

**Data sharing**

Not applicable

**Patient Involvement**

Not applicable

**Not commissioned; externally reviewed by Jeremy Chataway, London, UK.**

**Figure 1:**

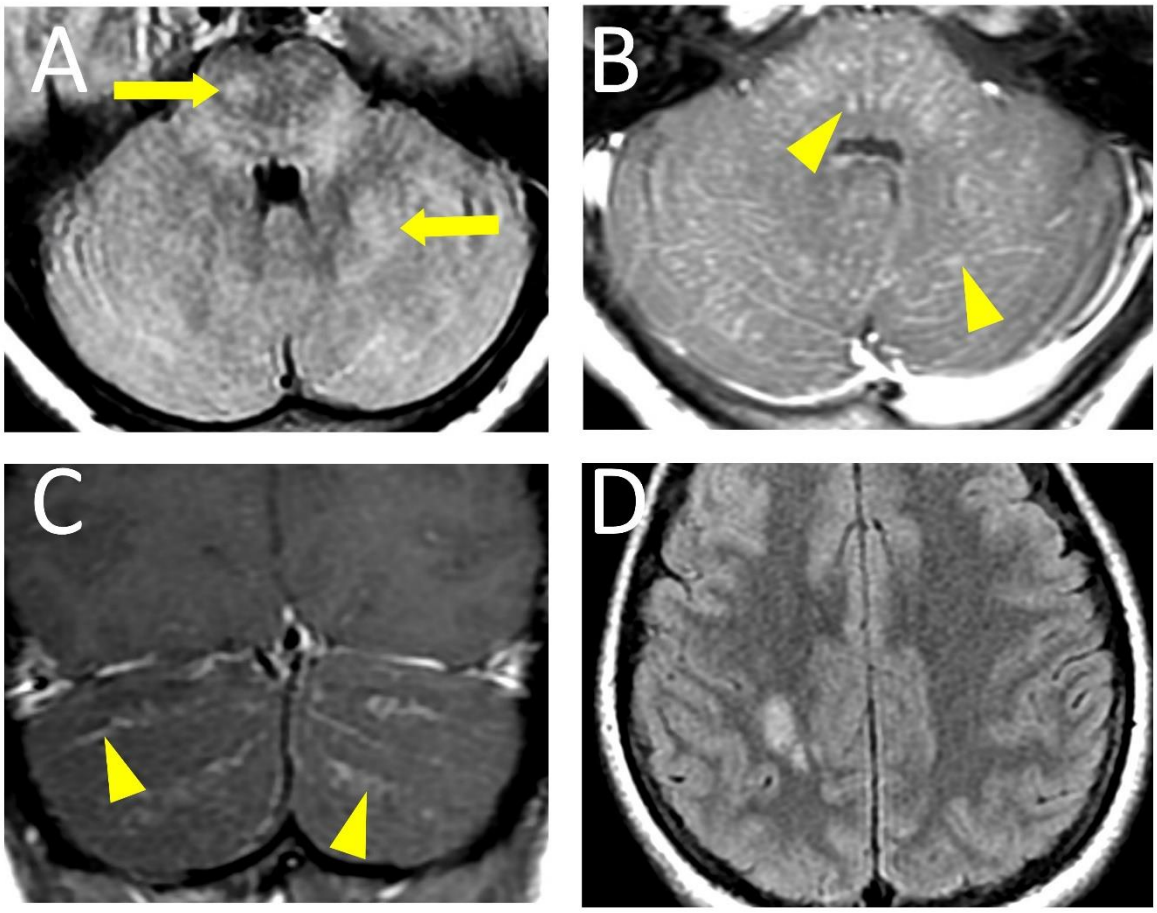

**Figure 2**

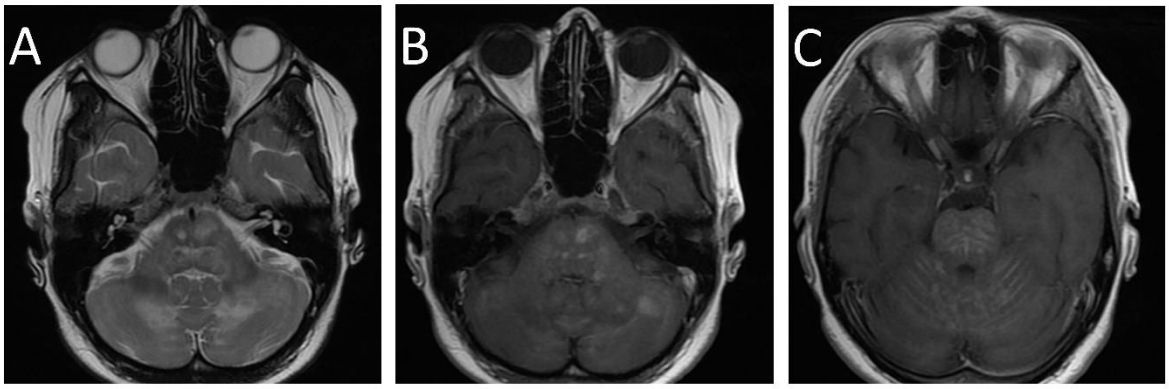


**Figure 3**

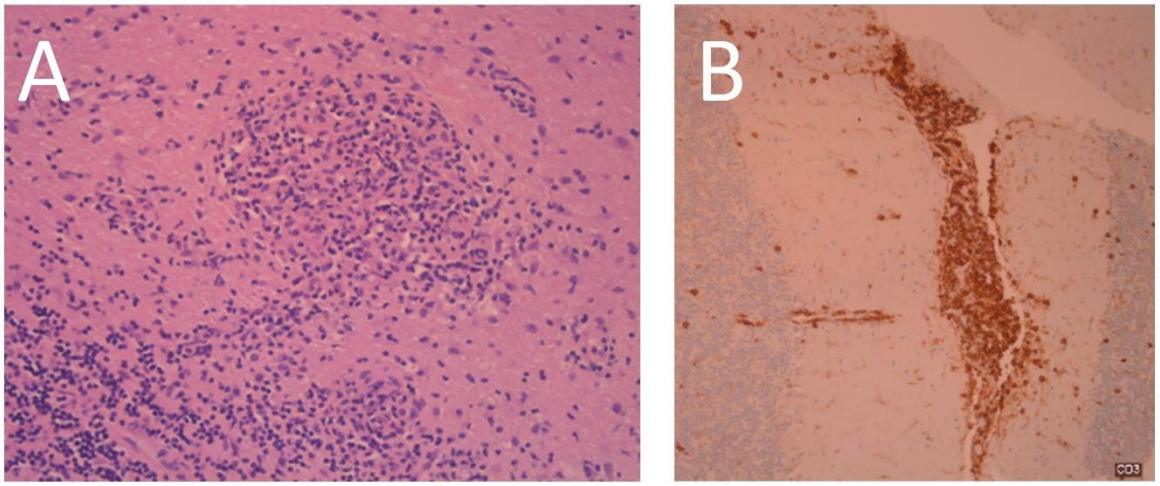

**Figure 4**