Summary

Isolated CNS presentations of Haemophagocytic lymphohistiocytosis (HLH), traditionally a systemic inflammatory condition, have been reported in adults and children. We identified nine patients with a diagnosis of isolated CNS familial HLH (fHLH) with symptom onset < 18 years of age, and one asymptomatic sibling. Children with atypical chronic/ recurrent CNS inflammation should be considered for immunological and genetic panel testing for fHLH even in the absence of any systemic inflammatory features. Despite haematopoietic stem cell transplantation (HSCT) being a mainstay of treatment, treatment failure and high morbidity and mortality post HSCT, suggest that alternative immune therapies may be worth considering.

Introduction

Haemophagocytic lymphohistiocytosis (HLH) has traditionally been thought of as a systemic inflammatory condition, characterised by cytokine storm and multiorgan dysfunction. The aetiology may be a primary genetic condition (familial HLH) or a secondary trigger such as infection, autoimmune disease, or malignancy. Current diagnostic criteria of systemic HLH[1] require at least five of the eight cardinal features; fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, haemophagocytosis, low/absent NK-cell-activity, hyperferritinemia and high-soluble interleukin-2-receptor levels. More recently isolated CNS presentations were also reported[2].

Here, we describe nince paediatric patients and one one asymptomatic sibling with an atypical neuroinflammatory condition with no features of systemic inflammation initially. All patients were found to have pathogenic variants associated with fHLH.

Methods

Patients were identified from UK–Childhood Neuroinflammatory Disease (UK-CNID) network from 2009 to 2021. Only patients with a confirmed genetic diagnosis were included. Patient with systemic involvement at onset were excluded. Demographics, clinical and paraclinical parameters were reviewed. The quantitative data are presented as median (interquartile range [IQR]), and the qualitative data are presented as number and frequencies or percentages. This study was approved by Great Ormond Street Hospital Research and Development Department (reference 16NC10).

Results

A total of nine patients (6 male) with a diagnosis of isolated CNS familial HLH with symptom onset before the age of 18 years, and one male asymptomatic sibling were identified. Table 1 and Figure 1 summarise the clinical, paraclinical and imaging features. Three patients have been reported elsewhere[3-5]. A full description of all the patients is provided in supplementary material (case vignettes).

Age at symptom onset was 2–15 years (median 8.5 years); 8 patients were Caucasian and 2 of South Asian ethnicity (Table 1). Three patients had underlying learning difficulties or developmental delay. Presenting neurological symptoms included cerebellar signs (n=5), headaches (n=3), seizures (n=3), convergent squint (n=3), optic neuritis (n=2), motor weakness (n=2) and cranial nerve palsies (n=2).

At disease onset, full blood count (FBC) was normal in all patients except 1 with thrombocytopenia. Ferritin and triglycerides were raised in 2/10 patients, and fibrinogen reduced in 2/10 children. Granule release assay was abnormal in 4/10 patients, and 4/10 patients had abnormal perforin expression and/or abnormal natural killer (NK) cell function. None of the patients met systemic HLH criteria at disease onset. Seven patients had serum MOG and AQP4 antibodies tested; all were negative. Intrathecal oligoclonal bands were detected in 3/10 patients, one additional patient had matched bands. CSF protein was raised in 4/10 patients (range 0.2-2.1 g/L) and total pterins were raised in 6/10 patients (range 78-525 nmol/L). Patients were empirically investigated by their physicians to exclude a range of alternative inflammatory and neurometabolic aetiologies.

During the disease course, three patients developed seizures, three had progressive ataxia, 1 had bilateral optic atrophy, 1 developed hemiparesis, 1 had recurrent transient ischaemic attack (TIA)-like events, and 1 had lower limb spasticity. In terms of disease course, six patients developed non-CNS disease progression and/or complications; recurrent fevers/febrile neutropenia (n=3), EBV/adenovirus viraemia (n=2), pneumocystis (n=1), pancreatitis (n=1), dermatological/cutaneous involvement (n=1), pericardial effusion (n=1) and chronic renal failure (n=1).

Baseline and follow-up neuroimaging is shown for the 9 symptomatic patients in figure 1. Six patients had neuroimaging findings at presentation typical of 'Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids' (patients 2, 3, 4, 6, 8 and 9), of which 2 children (patients 2 and 4) had additional supratentorial involvement on MRI at onset or on serial imaging. Lesional brain biopsy was performed in 3 patients; patient 1 had two biopsies showing perivascular chronic inflammatory process with non-specific CD8 infiltrates; patient 3 had prominent perivascular lymphocyte and macrophage infiltrates. Patient 6 had dense, predominantly T-cell Lymphohistiocytic inflammation of the leptomeninges, grey and white matter of submitted cerebellar tissue. One child had a skin biopsy which showed a cutaneous lymphoma.

Mutations involved in HLH were identified in all patients during follow-up; pathogenic variant of PRF1 gene (n=3), compound heterozygous mutations in UNC13D gene (n=2), inversion of Munc 13-4 gene (n=1), SH2D1A mutation gene (n=1), pathogenic variant in STXBP2 gene (n=1) and heterozygote likely pathogenic variant in RAB27A gene (n=2).

All 10 children were treated with steroids; IV methylprednisolone followed by oral prednisolone taper [n=8], oral prednisolone only [n=2]. Other immune therapies included intravenous immunoglobulin (n=6), mycophenolate mofetil (n=3), natalizumab (n=2), ciclosporin (n=1), cyclophosphamide (n=1), anakinra (n=1), tacrolimus (n=1), rituximab (n=1) azathioprine (n=1) and etoposide (n=1). Six patients underwent haematopoietic stem cell transplantation (HSCT); two had CNS relapse following this, and 1 had graft versus host disease (GvHD).

Three patients died during follow-up; 1 from CNS relapse post HSCT, 1 from presume treatment-related lung sepsis and one died suddenly from unexplained cause, one year after HSCT. Median EDSS in the seven surviving patients at last follow-up was 2 (range: 0-2).

Discussion

In this case series, we demonstrate that fHLH can present as an atypical neuroinflammatory condition, with striking neuroimaging findings, raised CSF protein and variable response to steroids early on in presentation or during disease course. This is consistent with two other cases series in children[6] and adults[7]. The mechanisms for how HLH causes CNS restricted neuroinflammation are not fully understood but may be related to functional defects in T lymphocyte and NK cell cytotoxicity causing impaired antigen clearance which occurs in systemic HLH[8].

A number of children in our series also had evidence of cerebellar, subcortical, optic pathway, pericallosal and spinal demyelination. Hence, there is a significant phenotypic overlap with Multiple Sclerosis (MS) and other acquired demyelinating conditions.

The presence of raised protein in the CSF, and prominent contrast enhancement on MRI may raise suspicion for fHLH. In addition, clinico-radiological discordance may be seen where extensive neuroimaging abnormalities are out of proportion to mild clinical signs and symptoms.

In all our cases there were no signs of systemic inflammation on initial presentation but in six cases inflammation meeting the criteria for systemic HLH became apparent over time. We propose that children with atypical chronic or recurrent CNS inflammation, especially presentations consistent with CLIPPERS should be considered for immunological and genetic panel testing for fHLH even in the absence of any systemic features of inflammation. By contrast to adult report of CLIPPERS[9], with and

without a confirmed fHLH mutation, there was a higher proportion of supratentorial involvement on initial and serial neuroimaging in our paediatric cohort.

The role of HSCT in genetically proven fHLH where the diagnostic criteria for systemic HLH are unmet remains controversial, above all in unaffected relatives with no neurological or systemic involvement. While it is recognised that fHLH can be fulminant and fatal at presentation, the long-term outcome after HSCT of children with neurological presentations of fHLH without systemic inflammation is not known. HSCT in itself is associated with significant morbidity and mortality and two cases in our series had a relapse of CNS neuroinflammation after HSCT. The role of newer immunomodulatory agents such as natalizumab or etanercept in halting disease activity is unclear but may be considered as alternative immune therapies to the current mainstay of treatment, HSCT. Earlier diagnosis and a better understanding of the pathobiological and genetic mechanisms of CNS HLH presentations will be crucial in effective therapies and eventually a better prognosis for patients.

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Legends

1. Male patient 1 presented at 2 years of age with severe encephalopathy and seizures, evolving movement disorders with no response to immune therapy. Baseline MRI scan (left) shows diffuse white matter signal abnormality in both cerebral hemispheres with further discrete lesions in the capsular white matter and brainstem. Multiple foci of contrast enhancement were shown on contrast administration. Follow-up imaging 7 months later (right) show severe atrophy with gliosis and a secondary left-sided subdural effusion.
2. Male patient 2 presented at 13 years of age with migraine-like episodes, followed by worsening ataxia, word findings difficulties, slurred speech and long tract signs two years later. Baseline MRI scan (left) show confluent white matter changes in both cerebral hemispheres with more focal capsular involvement. Further multiple punctiform and confluent lesions were noted in the pons and cerebellar peduncles also demonstrating contrast enhancement. Follow-up imaging 2 years later (right) shows parenchymal gliosis with persistent enhancing lesions noted in the posterior fossa.
3. Male patient 3 presented initially at 3 years of age with subacute ataxia, slurred speech, bilateral 6th nerve palsies, with neurological progression and relapses after multiple steroid courses. Baseline MRI scan (left) shows enhancing lesions in the posterior limbs of the internal capsules, brainstem and cerebellar peduncles. Follow-up imaging 12 years later (right) demonstrates parenchymal atrophy with mature gliotic scarring within the lesions but no enhancement.

4. Male patient 4 presented at 8 years of age with left convergent squint, ataxia and seizures. Baseline MRI scan (left) reveals an ill-defined mass-like enhancing lesion in the cerebellum and further small foci of abnormal signal in the cerebral white matter, with associated leptomeningeal enhancement in the cerebellum. Follow-up imaging 2 years later (right) shows diffuse parenchymal atrophy with more confluent cerebral white matter lesions and persisting mature injury within the cerebellum.
5. Female patient 5 presented at 14 years old with headaches, convergent squint, dysarthria, gait abnormality and hyperesthesia followed by seizures. Baseline MRI scan (left) demonstrates diffuse involvement of the posterior limbs of the internal capsule, periventricular white matter and patchy signal changes within the pons and cerebellum. There was associated leptomeningeal enhancement within cerebellum. Follow-up imaging 12 months later (right) reveals resolution of the white matter signal changes and progressive frontal parenchymal atrophy.
6. Male patient 6 presented at 4 years of age with nocturnal headaches followed by a squint with no response to steroids. Baseline MRI scan (left) reveals diffuse confluent deep and periventricular white matter abnormality in both cerebral hemispheres and cerebellar peduncles. There is faint enhancement of some of the cerebral lesions with leptomeningeal enhancement in the brainstem and hindbrain. Follow-up imaging 2 years later (right) shows mature gliotic injury within the cerebellum with persistent enhancing lesions.
7. Female patient 7 presented at 11 years old with ataxia, diplopia and strabismus and had worsening symptoms resistant to immune therapies. Baseline MRI scan (left) show multiple discrete lesions in the posterior limb of the internal capsule, brainstem and spine. These demonstrate contrast enhancement. Follow-up imaging 2 years later (right) demonstrates persistent enhancement of these lesions.
8. Male patient 8 presented at 9 years of age with subacute hemiplegia with progressive ataxia initially responsive to steroids, and relapsing once weaned. Baseline MRI scan (left) shows discrete periventricular and deep white matter lesions in both cerebral hemispheres and brainstem, with more confluent lesions involving the cerebellar peduncles. Punctiform contrast enhancement is noted in all lesions, with some demonstrating ring-like enhancement. Follow-up imaging 11 years later (right) shows residual lesions in the left corticospinal tract with mature injury within the cerebellar hemispheres, without contrast enhancement.
9. Female patient 9 presented at 9 years old with recurrent optic neuritis despite multiple immune therapies progressing to bilateral optic atrophy. Baseline MRI scan (left) shows moderately sized subcortical white matter lesions in both cerebral hemispheres with further discrete lesions

in the brainstem, cerebellar hemispheres and spinal cord. Follow-up imaging 3 years later (right) demonstrates faint enhancement was demonstrated in the cerebellar lesions, which also show maturational gliosis. The supratentorial lesions have resolved and no contrast enhancement is noted in any of the residual changes.