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Case Report

Familial Hemophagocytic Lymphohistiocytosis (Type 2) with solitary neurological presentation due to PRF1 gene mutation

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ABSTRACT

Familial hemophagocytic lymphohistiocytosis (FHLH) clinically manifest with fever, hepatosplenomegaly, pancytopenia, hyperferritenemia, hypofibrinogenemia and/or neurological signs. We report a case of solitary neurological presentation and absence of systemic signs of inflammation which was initially thought to be genetic leukodystrophy but latter turn out to be FHLH type 2 due to mutation in PRF1 gene. Pediatricians should keep FHLH as a differential diagnosis in a patient with solitary neurological presentation due to neuroinflammation even if no signs of systemic inflammation or abnormal laboratory parameters.

1. Introduction

Familial hemophagocytic lymphohistiocytosis (FHLH) is a systemic inflammation which presents by cytokine storm, multiorgan failure and high morbidity and mortality.[1] FHLH clinically manifest with fever, hepatosplenomegaly, hepatitis, pancytopenia, hyperferritenemia, hypertriglyceridemia, hypofibrinogenemia and/or neurological signs.[2] FHLH type 2 due to PRF 1 gene mutation can manifest during infancy or early childhood with solitary central nervous system (CNS) involvement due to neuroinflammation. CNS manifestations can be present initially or anytime during the course of disease.[3]

There were limited studies regarding solitary neurological presentation and FHLH. Here, we report a case of solitary neurological presentation due to neuroinflammation along with absence of systemic signs of inflammation and also lacked abnormal laboratory parameters for FHLH and which was initially thought be genetic leukodystrophy but latter turn out to be FHLH type 2 due to mutation in PRF1 gene.

2. Case Report

Three years boy born out of consanguineous marriage was apparently well till five months of age and then he presented with two episodes of febrile seizures two months apart. He also had motor milestones regression with progressive spasticity and language delay. The boy was admitted in our hospital for status epilepticus and managed with antiseizure drugs, ventilator care and supportive management. He responded well to treatment and was off ventilator within two days and was put on maintenance antiseizure drugs. His cerebrospinal fluid (CSF) examination and fundus examination were normal.

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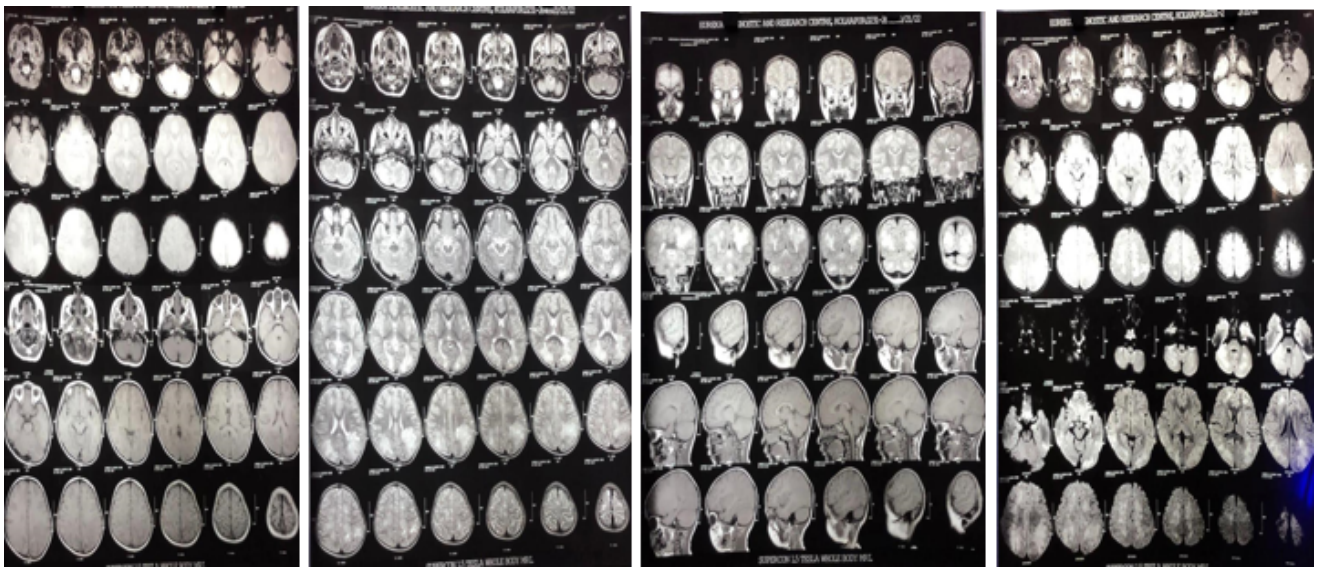
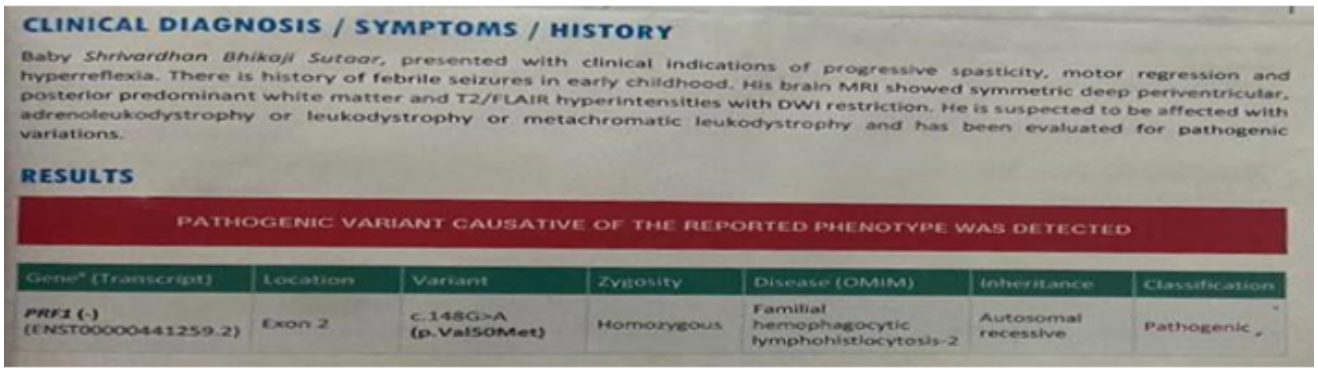


Fig. 1: MRI Images of patient suggestive of genetic leukodystrophy.



CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Baby *Shrivardhan Bhikaji Sutaar*, presented with clinical indications of progressive spasticity, motor regression and hyperreflexia. There is history of febrile seizures in early childhood. His brain MRI showed symmetric deep periventricular, posterior predominant white matter and T2/FLAIR hyperintensities with DWI restriction. He is suspected to be affected with adrenoleukodystrophy or leukodystrophy or metachromatic leukodystrophy and has been evaluated for pathogenic variations.

RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene* (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
PRF1 **(-)** (ENST00000441259.2)	Exon 2	c.148G>A (p.Val50Met)	Homozygous	Familial hemophagocytic lymphohistiocytosis-2	Autosomal recessive	Pathogenic

Fig. 2: Whole exome sequencing report suggestive of FHLH due to PRF1 gene mutation.

His clinical examination showed spasticity in all limbs (Lower limbs>upper limbs), exaggerated deep tendon reflexes, plantars upgoing and ankle contractures with scissoring posture. There were no hepatosplenomegaly and other systemic examination was normal. The laboratory parameters showed complete blood count (Hb 11gm, WBC 9200/cu.mm, Neutrophils 70% platelets 255000cu.mm), CRP 6 mg/l, ESR 12mm/hr and serum Ferritin 175 ng/ml. The liver function test and metabolic workup was normal. MRI Brain showed large areas signal abnormality in both cerebral hemispheres, predominantly involving white matter including the centra semiovale, parieto-occipital and frontal lobe. These areas appear hypointense and hyperintense on T1and T2 weighted images respectively along with patchy areas of restriction diffusion on Flair images. (Figure 1) These findings suggested the possibility of being secondary to an inherited metabolic disorder with dysmyelination such as adreno-leukodystrophy or metachromatic leukodystrophy. MRI spine was normal. In view of clinical presentation and MRI picture a possible diagnosis of genetic leukodystrophy was kept and genetic study, whole exome sequencing was ordered. To our surprise, it reported FHLH type 2, homozygous variant with gene PRF 1 and not any genetic leukodystrophy. (Figure 2) He was started with intrathecal methotrexate 10mg once 12 for weeks and injection hydrocortisone along with oral antiseizure drugs in maintenance doses and advised for hematopoietic stem cell transplantation (HSCT).

3. Discussion

FHLH is an autosomal recessive condition and known pathological gene mutations along with associated sub types include PRF1 (FHLH2), UNC12D (FHLH3), STX11 (FHLH4) and STXBP2 (FHLH5).[4] These mutations can affect Natural Killer cells and T lymphocytes to synthesize and release perforin (Protein product of PRF1) and granzymes. This results in dysregulation in immune

system.[3]

Our patient presented with solitary neurological presentation without any systemic signs of inflammation and also lacked laboratory parameters of inflammation but still genetic studies showed PRF1 gene mutation (FHLH type 2). Although neurological presentations are common at FHLH diagnosis, these rarely precede systemic manifestations. Feng Wei-Xing et al[3] reported four patients of FHLH in Chinese children who had only CNS presentation initially (seizures, coma, cranial palsies, ataxia, spasticity and gait abnormalities) and also missed the diagnosis as they thought of demyelinating condition like acute disseminated encephalomyelitis or multiple sclerosis. Aytac S et al[5] studied 73 patients FHLH and observed ten (25%) patients with isolated CNS involvement without any infectious trigger. These patients presented with unexplained neurological presentation and cranial nerve palsies leading to misdiagnosis and mistreatment. Yang et al[6] also found neurological symptoms in 13% children including seizures, coma, ataxia, hemiplegia and cranial nerve palsies. Similarly, in our patient also we misdiagnosed for leukodystrophy as our patient presented with spasticity mainly in lower limbs, gait abnormalities, motor regression and hyperreflexia along with seizures and also MRI picture is suggestive of genetic leukodystrophy.

Benson LA et al[7] also reported four patients with isolated neuroinflammation associated with FHLH and concluded that precise diagnosis and HSCT can decrease morbidity in CNS FHLH. Henter et al[1] suggested that FHLH diagnosis should not be made by only acquired hemophagocytic lymphohistiocytosis diagnostic criteria. Studies done by Horne et al[8] and Dias et al[9] found neurological presentation in 20-73% of FHLH patients and observed that the systemic presentation may present late as disease is still evolving.

CSF neopterin level is a useful biomarker for CNS FHLH disease activity among broad group of neuroinflammatory disorders.[10] But in our patient we could not able to do CSF neopterin level.

Our case report highlights that solitary CNS presentation due to neuroinflammation even in the absence of systemic inflammatory signs or normal laboratory parameters still can be FHLH.

4. Conclusion

Pediatricians should keep FHLH as a differential diagnosis in a patient with solitary neurological presentation due to neuroinflammation even if no signs of systemic inflammation or abnormal laboratory parameters. The genetic studies like whole exome sequencing should be ordered promptly for accurate diagnosis of FHLH.

5. Source of Funding

None.

6. Conflict of Interest

None.

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