

Genetic Hemophagocytic Lymphohistiocytosis with Syntaxin Gene Mutation

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ABSTRACT

We report a case of 5-year-old male who presented with off and on fever and bleeding. On examination he had oral ulcers and hepatosplenomegaly. One of his brothers who died at the age of one year, had similar complaints. Bone marrow examination of the child revealed hemophagocytosis. He was subsequently diagnosed as having Hemophagocytic Lymphohistiocytosis and next generation sequencing identified a rare 173T>C;p.Leu58Pro mutation in *STX11* genes in homozygous state resulting in familial or genetic HLH.

Keywords: Hemophagocytosis; Syntaxin gene mutation; Next generation sequencing

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life threatening disorder characterized by uncontrolled activation of T lymphocytes and macrophages leading to cytokine storm with multi organ involvement [1]. HLH can be familial or genetic and acquired. It maybe secondary to malignant disorders, autoimmune diseases and infections [1]. There are many genetic mutations associated with familial HLH. Most commonly reported mutations are found in Perforin gene. We present an interesting case of a rare genetic mutation causing HLH in a 5-year-old child.

CASE REPORT

A 5-year-old boy born to consanguineous parents was admitted in paediatric emergency department with history of high grade fever and bleeding from gums for the last 1 week. He also had fever which was associated with rigors and chills which were relieved by taking antipyretics.

There was significant decrease in oral intake for the last 14 days.

He had one alive healthy sibling and had history of one sibling's death an year back. Cause of death was not known but he was investigated by bone marrow examination, although no record was available.

There was no family history of any bleeding disorder.

Physical examination revealed a sick looking, pale child. He was febrile, had purpuric rash at the site of intravenous catheter

insertion. Oral cavity examination revealed coated tongue, congested throat and small size ulcers with healed margins on gums and lips. Abdominal examination revealed hepatosplenomegaly. Rest of the systemic examination was normal.

Full blood count of the child revealed pancytopenia. Hemoglobin 54 g/L, WBCs $2.4 \times 10^9/L$, Platelets $15 \times 10^9/L$. There was no atypical cell on peripheral smear examination. Absolute neutrophil count was 500/ μ l. Blood and urine cultures turned out to be negative. The child was started on empirical antibiotics. Liver function tests were deranged with ALT=82 U/L (NV=up to 41 U/L), AST=44 U/L (up to 39 U/L), C-reactive protein was 64 mg/dl. Urine complete examination revealed mild proteinuria and few pus cells. Bone marrow biopsy was planned which revealed prominent histiocytes showing hemophagocytic activity. Workup for primary and secondary hemophagocytosis was suggested which included serum ferritin, triglycerides, soluble CD25, Fibrinogen levels and NK cells activity. Serum ferritin turned out to be 10820 μ g/ml (normal value: Males 30-300 μ g/ml, Females 20-200 μ g/ml) while serum triglycerides were 346 mg/dl (normal value: up to 200 mg/dl). Soluble CD25 and NK cell activity were not done. Five out of eight criteria for the diagnosis of hemophagocytic lymphohistiocytosis (HLH) were fulfilled.

Keeping in mind the possibility of genetic or familial HLH, gene mutations Involving Perforin, Syntaxin, and other related genes was tested using next generation sequencing which identified a rare 173T>C;p.Leu58Pro mutation in *STX11* genes in homozygous state responsible for familial or genetic HLH.

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Child was referred to Pediatric oncology department of Children Hospital Lahore for further management according to HLH2004 protocol with Etoposide, cyclosporine A and intrathecal methotrexate. Patient was followed up with cyclosporine levels, serum ferritin, serum triglycerides. Patient was subsequently referred to hemopoietic stem cell transplant centre for stem cell transplant which is considered as the only curative treatment of genetic hemophagocytosis.

DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially life threatening disorder with fever and splenomegaly, cytopenias, raised serum ferritin, raised triglyceride levels, and reduced serum fibrinogen levels representing diagnostic criteria for HLH. Liver failure and neurological manifestations are also common clinical features [1,2].

This case is the first ever case of this mutation reported from Pakistan. This mutation is found in Turkish/Korean children with HLH. This case has a peculiar presentation. Mostly HLH presents in infancy, but the patient in this case has late onset. Diagnosis of HLH, as proposed by the Histiocyte Society, requires clinical, laboratory, and histopathologic features. Fever and splenomegaly are regarded as the most common clinical signs, but hepatomegaly, jaundice, and rash are also documented [1,2]. Of central nervous system abnormalities, encephalopathy, and seizures are the most common findings [2]. Investigation of familial cases have revealed autosomal recessive null mutations in different genes like *PRF1*, *STXBP2*, *STX11*, *RAB27A*, *UNC13D* and *LYST* which prevent target cell killing by cytotoxic T cells and natural killer cells and are invariably associated with manifestation of HLH in childhood [3]. Depending on the above mentioned genes, significant differences are seen in the average age at onset [3].

The various genetic mutations cause familial HLH with different disease presentations. Patients with *PRF1* mutations mostly have disease onset during infancy, whereas *STX11* mutations typically cause onset at older age as in the reported case [3]. Among patients with *STX11* mutations, nonsense mutation may cause presentation during infancy, while those with biallelic missense mutations present late [3].

If biallelic mutations in HLH-associated genes are detected, it warrants hematopoietic stem cell transplantation, which currently is the only curative treatment for inherited or primary HLH [4].

Secondary HLH is typically due to certain infections, which maybe bacterial, viral, parasitic, certain hematological malignancies, or autoimmune conditions. Few of these patients carry a heterozygous mutation in HLH-associated genes [4,5].

The findings by de Saint Basile and coworkers give the concept of a polygenic inheritance in case of HLH. A cohort of 2701 patients with clinically suspected HLH, Zhang and colleagues documented that only 1% of patients carried heterozygous mutations in different HLH causative genes [6]. Distinct HLH-associated genes result with different severities of the disease.

Many genome projects have even revealed that 16% of the population carries at least 1 damaging mutation in a gene needed for lymphocyte cytotoxicity [6].

CONCLUSION

It is therefore concluded that a child with fever, cytopenias and hepatosplenomegaly with no abnormal cell on peripheral smear should be investigated for genetic hemophagocytosis as timely diagnosis can guide appropriate and timely treatment. It can be hypothesized that disease-causing mutations in familial HLH have different phenotypes but mostly no particular ethnicity. This hypothesis can be tested in a study of different mutations and their effect on disease phenotype and onset [7].

CONFLICT OF INTEREST

The authors have no conflict of interests to disclose.

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