Novel Hexokinase 1 Genetic Mutation Presenting with Recurrent Fever and Developmental Delay: Possible Insight on the Role of Glucose Metabolism Dysregulation and Autoinflammation

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A B S T R A C T

Hexokinase 1 (HK1) is a key enzyme in the glycolytic pathway. Dysregulation of HK1 causes activation of NLRP3 inflammasome and subsequently overexpression of proinflammatory cytokines IL-1 B and IL-18. HK1 genetic mutation has been reported in cases of neurodevelopment abnormalities with visual impairment and nonspherocytic hemolytic anemia, but its role in recurrent fever and systemic inflammation has not been reported yet. We present a case of an early childhood boy with a history of developmental delay who experienced recurrent episodes of high-grade fever, responding partially to antipyretics and antibiotics, with abdominal pain but no skin rash or joint pain. Whole exome sequencing revealed a novel heterozygous variant in HK1 (c.2198C>T; p. Ser733Phe), which is predicted to have a potentially deleterious effect based on PolyPhen-2 and SIFT In silico analyses. This case report highlights the possible new association of autoinflammation and HK1 mutation in addition to typical features such as neurodevelopmental delay and anemia.

Keywords: Hexokinase1; Autoinflammation; Neurodevelopmental; Anemia; Recurrent fever

Abbreviations: HK1: Hexokinase 1; NLRP3: nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; SIFT: Sorting Intolerant From Tolerant; SAD: Systemic autoinflammatory diseases; ATP: adenosine triphosphate; ADP: adenosine diphosphate; G6P: glucose-6-phosphate; NAG: N-acetylglucosamine; CNS: central nervous system

Introduction

Systemic autoinflammatory diseases (SAD), also known as periodic fever syndromes, are a group of disorders with an increasing prevalence that arise from dysregulation of the innate immune system1. These disorders typically present with recurring fevers and inflammation without any obvious trigger1. Many SAD patients have pathological genetic variants contributing to systemic inflammation2. In the last three years, the number of autoinflammatory diseases due to monogenic defects has increased from 42 disorders to 56 disorders based on the updated classification by the International Union of Immunological Societies in 20223. Identifying new genetic defects in SAD patients has allowed for a better understanding of the underlying immunological mechanisms, thus opening new perspectives in targeted therapies.
The activation of the NLRP3 (nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3) inflammasome plays an essential role in host defense against microbial infections. However, its dysregulated activation can lead to several autoimmune inflammatory disorders. Hexokinase, a key enzyme in the glycolytic pathway, can be released from mitochondria and activates NLRP3 upon exposure to N-acetylglucosamine, which is bacterial-derived peptidoglycan. The activation of NLRP3 inflammasome activation results in the secretion of IL-1B and IL-18, leading to an inflammatory response. In this report, we present a case of an early childhood boy with developmental delay who experienced recurrent episodes of high-grade fever with abdominal pain in the absence of clear evidence of infection or malignancy. Whole exome sequencing revealed a novel heterozygous variant in HK1 (c.2198C>T; p. Ser733Phe). The results revealed a novel heterozygous variant in Exon/Intron sequencing revealed a novel heterozygous variant in HK1 (c.2198C>T; p. Ser733Phe).

Case Presentation

We report the case of an early childhood boy who was born to healthy non-consanguineous parents via spontaneous vaginal delivery at full term with a birth weight of 2.0 kg. At eight months of age, he was admitted to the hospital with a seizure and was diagnosed with aseptic meningitis. The cerebrospinal fluid analysis showed negative bacterial culture, leukocyte count of 10, glucose of 4 mmol/L, and protein of 21.0 mg/dL. An abnormal Electroencephalogram with epileptiform brain activity was also identified. He was discharged home on antiepileptics. Subsequently, The patient was noted to have delayed developmental milestones. He rolled over at 12 months of age, sat up at 18 months of age, and walked at the age of 30 months. He started to have recurrent episodes of high-grade fevers at the age of 1 year. Each episode lasted 4-5 days and responded partially to antipyretics and oral antibiotics. The interval between fever attacks was irregular, sometimes only a few days apart. The patient was entirely well between the episodes of fevers. These fever attacks were associated with abdominal pain. He had no history of skin rash, joint pain, or symptoms suggestive of respiratory or urinary infections. There was no family history of periodic fevers, arthritis, or renal failure. Physical assessment at the age of 4 years revealed a well-appearing non-dysmorphic child. His temperature was 38.8°C, and other vital signs were normal. His weight was 14 kg (25th percentile), height 98 cm (25th percentile), and head circumference 50 cm (50th percentile). A delay in fine and gross motor development was noted. There was no rash, lymphadenopathy, or other significant findings on physical examination.

Complete blood count revealed normal white blood cell counts, normochromic microcytic anemia (hemoglobin 10.2 g/dl), and thrombocytosis (platelet counts 525 X 10^9/μl). The platelet count returned to normal between attacks. Iron profile was low and peripheral blood smear suggested iron deficiency anemia. Liver and renal function tests were normal. Erythrocytes sedimentation rate was 83 mm/h and remained high between attacks. C-reactive protein was 3.0 mg/dl. Screening for infectious causes was negative and Immunoglobulins levels were normal. Eyes examination by slit lamp was normal. Abdominal ultrasonography showed mesenteric lymphadenitis and mild ascites. Echocardiogram was normal. The hearing assessment was normal. Upon suspicion of periodic fever syndromes, a commercially available whole exome sequence was performed. The results revealed a novel heterozygous variant in Exon/Intron 15 of HK1 (c.2198C>T; p. Ser733Phe), which is predicted to have a potentially deleterious effect based on PolyPhen-2 and SIFT In silico analyses.

Discussion

Our patient was diagnosed with HK 1 genetic mutation by genetic testing, ordered in the setting of recurrent fever, development delay, and family history of consanguinity. HK1 is a crucial glucose metabolism enzyme located on the mitochondrial cell wall. It phosphorylates hexoses (six-carbon sugar) to hexose 6 phosphate by utilizing a phosphate from the conversion of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) (Figure 1). Glucose is the primary substrate for HK1 and glucose-6-phosphate (G6P) is the major product (Figure1).

![Figure 1: Hexokinases are crucial enzymes involved in glucose metabolism. They phosphorylate hexoses (six-carbon sugar) to hexose 6 phosphate by utilizing a phosphate from the conversion of adenosine triphosphate (ATP) to adenosine diphosphate (ADP).](image)

Phosphorylation of glucose to G6P by HK1 facilitates glucose transport into cells. Four major HK isozymes have been described in humans, each encoded by a distinct gene and expressed in different tissues. HK1 is expressed in multiple normal tissues, including erythrocytes, brain, and fibroblasts, as well as in abnormal cells such as malignant tissues. HK1 is also expressed in white blood cells, particularly monocytes, and plays a significant role in glucose metabolism, which serves as a crucial source of energy for monocytes and neutrophils. Besides its involvement in energy utilization and the survival of mononuclear cells, HK1 also plays a vital role in cell signaling and protection against pathogens. Dysregulation in HK1 enzyme activity affects these cells leading to the activation of the NLRP3 inflammasome (Figure 2).

![Figure 2: Hexokinase 1 (HK1) binds to N-acetylglucosamine (NAG) and dissociates from the mitochondria. The dissociation of HK1 from mitochondria is enough to induce the activation of the NLRP3 inflammasome and the production of IL-1β.](image)
HK1 has the ability to function as an innate immune sensor by binding to N-acetylglucosamine (NAG), a peptidoglycan subunit derived from a gram-positive bacterial cell wall. The binding of NAG to HK1 inhibits its activity and leads to the dissociation of HK1 from mitochondria. The dissociation of HK1 from mitochondria is enough to induce the activation of the NLRP3 inflammasome and the production of IL-1β. It is plausible that the novel HK1 mutation (c.2198C>T; p.Ser733Phe) in our patient results in the spontaneous dissociation of HK1 from mitochondria, potentially triggering inflammation. However, further experimental studies are required to confirm this hypothesis.

Traditionally, HK1 deficiency has been associated with autosomal recessive early-onset severe nonphosphorycetic hemolytic anemia caused by an impaired glycolytic pathway in red cell metabolism. However, additional phenotypes have emerged over time, including Hereditary Motor and Sensory Neuropathy-Russe, retinitis pigmentosa, and neurodevelopmental disorder. In cases where patients exhibited neurodevelopmental abnormalities and visual impairment, HK1 mutations were inherited in an autosomal dominant manner and were not accompanied by hemolytic anemia. Furthermore, the activity of HK1 in the red blood cells of two patients was found to be normal, indicating that the neurological manifestations were not due to a loss of hexokinase enzymatic activity. Similarly, Sullivan et al. identified a large six-generation family with autosomal dominant retinitis pigmentosa caused by a heterozygous HK1 mutation (p.Glu847Lys) without evidence of hemolytic anemia. Our patient had a novel HK1 mutation (c.2198C>T; p.Ser733Phe) which presented with recurrent fever and neurological features but no evidence of hemolysis. While the neurological manifestations in this case are likely attributed to the direct metabolic effects of HK deficiency, it is plausible that some features may be influenced by an inflammatory response in the brain. For example, certain autoinflammatory disorders are well recognized for their central nervous system involvement, and other diseases had CNS features as a recent expansion in their phenotypic presentation. Additionally, CNS involvement can be only sign of autoinflammatory disorder on presentation as the sole initial sign of an autoinflammatory condition, CNS involvement can be the only sign of autoinflammatory condition initially. Lastly, a growing body of evidence supports the role of neuroinflammation in the development of neurodegenerative diseases such as Alzheimer’s and Parkinson’s disease.

Conclusion

In summary, our patient exhibited an autoinflammatory phenotype characterized by recurrent fever and elevated inflammatory markers in the absence of an infectious trigger. This expands the disease phenotype associated with HK1 mutations.

References


