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Case Report

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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ABSTRACT

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 system[1]. These disorders typically present with recurring fevers and inflammation without any obvious trigger[1]. Many SAD patients have pathological genetic variants contributing to systemic inflammation[2]. 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 2022[3]. 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 autoinflammatory disorders[4]. 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[5]. 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).

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 centile), height 98 cm (25th centile), and head circumference 50 cm (50th centile). 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 10^3/UI). 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 83mm/h and remained high between attacks. C-reactive protein was 3.0mg/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 susception 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)**.

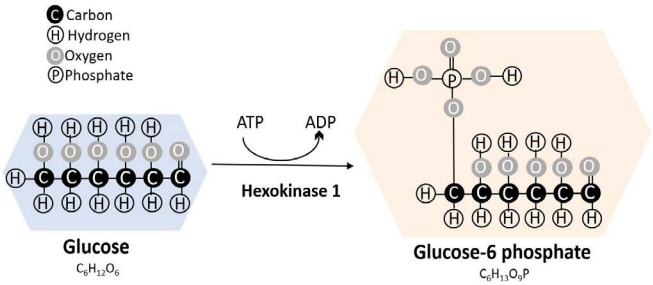

Figure 1: Hexokinases are crucial enzymes involved in glucose metabolism. They phosphorylate hexoses (six-carbon sugar) to hexose 6 phosphate by utilizing a phosphate from the conversion of adenosine triphosphate (ATP) to adenosine diphosphate (ADP).

Phosphorylation of glucose to G6P by HK1 facilitates glucose transport into cells[6]. Four major HK isozymes have been described in humans, each encoded by a distinct gene and expressed in different tissues[6]. HK1 is expressed in multiple normal tissues, including erythrocytes, brain, and fibroblasts, as well as in abnormal cells such as malignant tissues[7,8]. 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[9,10]. 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[5,9]. Dysregulation in HK1 enzyme activity affects these cells leading to the activation of the NLRP3 inflammasome[5] **(Figure 2)**.

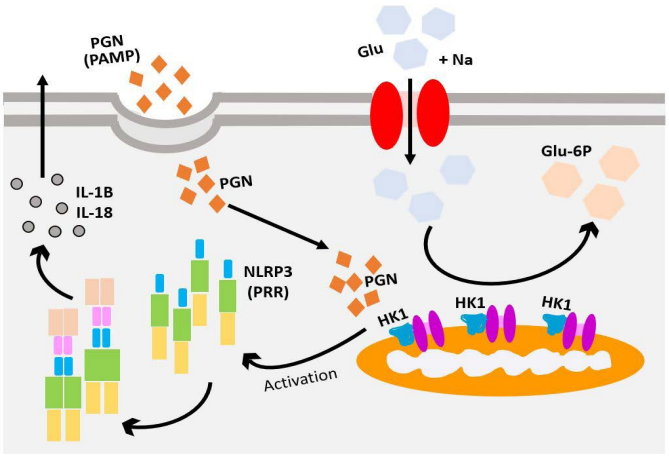

Figure 2: Hexokinase 1 (HK1) binds to N-acetylglucosamine (NAG) and dissociates from the mitochondria. The dissociation of HK1 from mitochondria is enough to induce the activation of the NLRP3 inflammasome and the production of IL-1β.

NLRP3, a high-molecular-weight protein located on the long arm of chromosome 1[11], is a Pattern Recognition Receptor that recognizes Pathogen Associated Molecular Patterns[12]. NLRP3 gain of function mutation leads to the autoactivation of the inflammasome pathway and subsequent secretion of IL-1, resulting in cryopyrin-associated periodic fever syndromes[11]. Anakinra (Kineret), rilonacept (Arcalyst), and canakinumab (Ilaris) are medications that inhibit the activity of IL-1β and lead to the improvement of symptoms and a decrease in systemic inflammation[13].

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[14]. The binding of NAG to HK1 inhibits its activity and leads to the dissociation of HK1 from mitochondria[5]. The dissociation of HK1 from mitochondria is enough to induce the activation of the NLRP3 inflammasome and the production of IL-1β[5]. 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 nonspherocytic hemolytic anemia caused by an impaired glycolytic pathway in red cell metabolism[15,16]. However, additional phenotypes have emerged over time, including Hereditary Motor and Sensory Neuropathy-Russe[17], retinitis pigmentosa[18], and neurodevelopmental disorder[19]. 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[19]. 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[18]. 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 (CNS) involvement[20], and other diseases had CNS features as a recent expansion in their phenotypic presentation[21]. Additionally, CNS involvement can be only sign of autoinflammatory disorder on presentation[22] 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[23].

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. The autoinflammatory aspect of the disease may be unique to this novel mutation (c.2198C>T; p.Ser733Phe) and its impact on NLRP3 signaling, although further validation is required through experimental animal models. This case highlights the importance of genetic testing in patients presenting with neurological sequelae and recurrent fever, as it can provide crucial insights into the underlying genetic basis of the condition.

Declarations

Ethics approval and consent to participate: ethical approval was obtained from the biomedical research ethics committee at Umm Al-Qura University (Approval No: HAPO-02-K-012-2024-02-2063). Written informed consent was obtained from the parent.

Authors' contributions: Aisha Mirza wrote the initial draft and created the figures. Husni Rayes reviewed and edited the manuscript. Heba AlQurashi reviewed and edited the manuscript. Amer Khojah wrote the conclusion and edited the manuscript.

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Consent for publication: Consent for publication was obtained from the parent.

Availability of data and material: Data and material will be available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no conflicts of interest related to this research.

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References

1. Krainer J, Siebenhandl S, Weinhausel A. Systemic autoinflammatory diseases. J Autoimmun 2020;109:102421.
2. Demir F, Dogan OA, Demirkol YK, et al. Genetic panel screening in patients with clinically unclassified systemic autoinflammatory diseases. Clin Rheumatol 2020;39(12):3733-3745.
3. Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity: 2022 Update on the classification from the international union of immunological societies expert committee. J Clin Immunol 2022;42(7):1473-1507.
4. Blevins HM, Xu Y, Biby S, Zhang S. The NLRP3 inflammasome pathway: A review of mechanisms and inhibitors for the treatment of inflammatory diseases. Front Aging Neurosci 2022;14:879021.
5. Wolf AJ, Reyes CN, Liang W, et al. Hexokinase is an innate immune receptor for the detection of bacterial peptidoglycan. Cell 2016;166(3):624-636.
6. Kanno H. Hexokinase: Gene structure and mutations. Best Practice Research Clinical Haematology 2000;13(1):83-88.
7. Shinohara Y. [Identification and characterization of hexokinase isozyme predominantly expressed in malignant tumor cells]. Yakugaku Zasshi 2000;120(8):657-666.
8. Wilson JE. Isozymes of mammalian hexokinase: Structure, subcellular localization and metabolic function. J Exp Biol 2003;206(12):2049-2057.
9. Sen S, Kaminiski R, Deshmane S, et al. Role of hexokinase-1 in the survival of HIV-1-infected macrophages. Cell Cycle 2015;14(7):980-989.
10. Pithon-Curi TC, De Melo MP, Curi R. Glucose and glutamine utilization by rat lymphocytes, monocytes and neutrophils in culture: a comparative study. Cell Biochem Funct 2004;22(5):321-326.

11. Hoffman HM, Wright FA, Broide DH, Wanderer AA, Kolodner RD. Identification of a locus on chromosome 1q44 for familial cold urticaria. Am J Hum Genet 2000;66(5):1693-1698.

12. Martinon F. Detection of immune danger signals by NALP3. J Leukoc Biol 2008;83(3):507-511.

13. Romano M, Arici ZS, Piskin D, et al. The 2021 EULAR/American College of Rheumatology points to consider for diagnosis, management and monitoring of the interleukin-1 mediated autoinflammatory diseases: cryopyrin-associated periodic syndromes, tumour necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the interleukin-1 receptor antagonist. Ann Rheum Dis 2022;81(7):907-921.

14. O'Sullivan D, Kelly B, Pearce EL. When Hexokinase Gets that NAG-ing Feeling. Cell Metab 2016;24(2):198-200.

15. Bianchi M, Magnani M. Hexokinase mutations that produce nonspherocytic hemolytic anemia. Blood Cells Mol Dis 1995;21(1):2-8.

16. van Wijk R, Rijksen G, Huizinga EG, Nieuwenhuis HK, van Solinge WW. HK Utrecht: Missense mutation in the active site of human hexokinase associated with hexokinase deficiency and severe nonspherocytic hemolytic anemia. Blood 2003;101(1):345-347.

17. Hantke J, Chandler D, King R, et al. A mutation in an alternative untranslated exon of hexokinase 1 associated with Hereditary Motor and Sensory Neuropathy-Russe (HMSNR). Eur J Human Genetics 2009;17(12):1606-1614.

18. Sullivan LS, Koboldt DC, Bowne SJ, et al. A dominant mutation in hexokinase 1 (HK1) causes retinitis pigmentosa. Invest Ophthalmol Vis Sci 2014;55(11):7147-7158.

19. Okur V, Cho MT, van Wijk R, et al. De novo variants in HK1 associated with neurodevelopmental abnormalities and visual impairment. Eur J Hum Genet 2019;27(7):1081-1089.

20. Uccelli A, Gattorno M. Neurological manifestations in autoinflammatory diseases. Clin Exp Rheumatol 2018;36 (1):61-67.

21. Khojah A, Gunderman L, Bukhari A, Schutt M, Cohran V. Early-onset Crohn's disease, IgA nephropathy, and hemophagocytic lymphohistiocytosis in a patient with IL-10 receptor deficiency. Clin Immunol Communications 2022;2:145-148.

22. Blincoe A, Heeg M, Campbell PK, et al. Neuroinflammatory Disease as an Isolated Manifestation of Hemophagocytic Lymphohistiocytosis. J Clin Immunol 2020;40(6):901-916.

23. Kwon HS, Koh S-H. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. Translational Neurodegeneration 2020;9(1):42.