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CASE REPORT

Tyrosinemia type I: an unusual case presentation

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ABSTRACT

Background: Hereditary tyrosinemia type 1 (HT1) is an autosomal recessive inherited metabolic disorder caused by the fumerylacetoacetate hydrolase enzyme deficiency. It is characterized by liver dysfunction and/or failure, renal tubular dysfunction. If left untreated it may lead to Fanconi syndrome and neurological crisis (porphyria-like crisis). Nitisinone is the recommended therapy for HT1 in combination with tyrosine and phenylalanine restricted diet.

Case Presentation: In this report, we present 3 years and 8-months-old boy who was referred to the Metabolic Clinic after his cousin was diagnosed with HT1. His history was significant for pleural effusion at 8 months of age which contributed to pulmonary tuberculosis. His alpha-fetoprotein was checked (for no apparent reason) at one and a half years of age and was elevated. Upon evaluation at 3 years and 8 months at our facility, his succinylacetone was significantly elevated. Liver function tests and coagulation results were also mildly elevated. Liver ultrasound was routine apart from gallstones. Targeted mutation testing revealed a fumarylacetoacetate hydrolase gene's homozygous pathogenic variant (c.982C>T; p. Gln328*).

Conclusion: In conclusion, we presented a patient with an unusual, late presentation of HT1, to highlight the clinical variability in this rare, treatable metabolic disease.

Keywords: Tyrosinemia type I, Hereditary tyrosinemia type 1, nitisinone, FAH, fumarylacetoacetate hydrolase.

Introduction

The tyrosine degradation pathway consists of five enzymes associated with known inherited metabolic disorders, the most severe of which is hereditary tyrosinemia type 1 (HT1; OMIM 276700). HT1 is an autosomal recessive disease caused by a deficiency of fumarylacetoacetate hydrolase (FAH), the last enzyme of the tyrosine degradation pathway. Although it is a rare disease worldwide, HT1 shows higher incidence in some populations due to the founder effect (1,2). The deficiency of FAH results in the accumulation of proximal metabolites such as maleylacetoacetate (MAA), fumarylacetoacetate (FAA), as well as their derivatives; succinylacetoacetate and succinylacetone (SA). These metabolites can react with thiol groups in proteins, such as glutathione, causing serious DNA damage, leading to several manifestations encountered in HT1, including liver cirrhosis and renal tubular dysfunction, which may present as renal Fanconi syndrome or renal failure. SA is also a potent inhibitor of the enzyme 5-aminolevulinic acid (5-ALA) dehydratase, resulting in accumulation of 5-ALA, which is thought to be responsible for the acute neurological crisis seen in patients with HT1 (2,3). Hypertyrosinemia is also observed in HT1, but elevated tyrosine levels can also be seen in different clinical situations such as liver failure from any cause, transient tyrosinemia of the newborns, and liver immaturity in premature babies (4). The clinical presentation of HT1 is widely variable, and affected individuals can present from infancy to adulthood, although presentation after 2 years is rare. HT1 can be categorized into three main clinical categories as follows: acute, subacute, and chronic. The onset of the acute form of HT1 is usually before 2 months of age in the form of severe liver impairment associated with hepato -and splenomegaly, abnormal coagulation profile, and hypoglycemia which can be severe enough if untreated to lead to cirrhosis and death in the first months of life (1,2). The subacute form of HT1 presents later, between 6 months and 1 year of age, with liver disease, coagulopathy, failure

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to thrive, hypotonia, hepatosplenomegaly, and rickets. The chronic form usually presents after 6 months of age with a less aggressive clinical picture, including proximal tubulopathy leading to Fanconi syndrome, cardiomyopathy, growth retardation, and neurological crisis, which may last a few days (1,3). HT1 is one of the most known inborn error of metabolism (IEM) with the highest incidence of malignancy transformation (hepatocellular carcinoma) (1). Nitisinone [2-(2-nitro-4-trifluoro-methylbenzyol)-1,3 cyclohexanedione] is the standard treatment for HT1. It acts by inhibiting the second enzyme in the tyrosine degradation pathway, parahydroxyphenylpyruvic acid dioxygenase. This will prevent the accumulation of toxic metabolites, FAA and MAA and their derivative, SA (1,5). Nitisinone treatment should begin as soon as possible once the diagnosis of HT1 has been confirmed (5). As nitisinone increases the concentration of tyrosine, a diet restricted in phenylalanine and tyrosine should be started to prevent tyrosine accumulation, resulting in crystals formation in the cornea. Liver transplantation should be reserved for those with severe liver failure at presentation and who failed to respond to nitisinone therapy or have evidence of malignant changes in the liver (6). In this report, we present the clinical, biochemical, and molecular findings of 3 years and 8 months old boy who was presented with an unusual, late presentation of HT1 along with a classical presentation in his cousin with the same genotype. A retrospective chart review was conducted in reporting this case. The CARE guidelines were followed in reporting this case.

Case Presentation

The subject is 3 years and 8 months old boy who was born at full term following uncomplicated pregnancy and delivery. Newborn screening (NBS) was normal although HT1 was not included in the local NBS program. Family history was positive for consanguinity, and he was the first child in the family and has one younger sister, currently 2 years old, and healthy. The patient was well till the age of 8 months when he developed fever and respiratory distress and was found to have pleural effusion, and he was diagnosed at that time to have pulmonary tuberculosis. He was treated with anti-tuberculosis medications for 8 months. During his follow-up, he was found to have a high alpha-fetoprotein level (AFP) and mildly elevated transaminases, but this was not investigated further. He continued to do well, and by the age of 3 years and 8 months, he was referred to our service after his cousin was diagnosed with HT1 at the age of 6 months to rule out the possibility of having the same disease with a different presentation.

The cousin was a girl who was presented at the age of 6 months with abdominal distention, hepatosplenomegaly, pancytopenia, and coagulopathy with mildly high liver transaminases. She was hospitalized for further workup and found an elevated SA level (9.2 umol/l; reference range 0-1.5 umol/l). Subsequently, she was started on nitisinone, as well as a diet restricted with tyrosine. The diagnosis of HT1 was confirmed molecularly, and the patient was found to have a homozygous nonsense variant in the FAH gene (c.982C>T p. Gln328* (NM_000137.2). The patient continued to show normal growth and development on treatment.

Going back to our subject, his first evaluation at our clinic was at 3 years and 8 months of age showed high tyrosine level (767 umol/l, cut-off value < 200 umol/l), elevated dry blood spot SA level (31.6 umol/l; reference range 0-1.5 umol/l). Serum AFP level was also significantly elevated at 2,416.1 ng/ml (reference range 0.89-8.78 ng/ml) while transaminases were mildly elevated (alanine amino transferase = 213 µ/l reference range 0-55 µ/l, aspartate amino transferase = 133 µ/l reference range 5-34 µ/l). There was mild coagulopathy [partial thromboplastin time (PTT)]: 47.80 seconds (reference range 25.3-38.3 seconds), prothrombin time (PT): 17.5 seconds (reference range 9.7-12.6 seconds), and International Normalized Ratio (INR) = 1.5 (reference range 0.81-1.23 seconds). Further evaluation showed a normal skeletal survey with good bone density, and abdominal ultrasound of the liver revealed only multiple gallstones with no acute cholecystitis. Molecular testing by targeted mutation analysis showed a homozygous pathogenic variant in FAH gene c.982C>T p. Gln328* (NM_000137.2). The patient was started on nitisinone, which resulted in normalization of his biochemical profile 3 months later; SA level normalized while AFP dropped to 211.8 ng/ml. Coagulopathy also resolved (PT = 12.5 seconds, PTT = 38.70 seconds INR = 1.08). By the age of 4 years and a half, the patient developed right focal seizures with ictal and postictal transient blindness bilaterally. His first episode was in the form of status epilepticus for around 20 minutes, tonic- colonic affecting the right side of the body, associated with loss of consciousness with upward gaze. Post-ictal weakness was noted at first attack requiring physiotherapy to attain baseline function of lower limbs. Brain magnetic resonance imaging showed no acute changes. Afterward, the patient continued to have frequent seizures with the same semiology and postictal blindness almost once per month but not as long as the initial attack. He was followed by the neurology, and his seizure was well controlled after starting anti-epileptic medications. Currently, at the age of 6 years, the patient has been seizure free for the last 2 years, with no neurological signs. Also, the patient continued to have normal cognition and normal growth parameters. His weight is on the 97th centile, and his height is on the 50th centile. He has normal development for age.

Discussion

HT1 is an autosomal recessive inherited metabolic disease caused by a deficiency of the FAH enzyme, the last enzyme in the tyrosine catabolic pathway. HT1 is characterized, if untreated, by progressive liver impairment, renal tubular dysfunction, increased risk of hepatocellular carcinoma, and neurological crises (7,8). HT1 can be categorized based on the age of onset into three categories: acute type, subacute, and chronic type. In this report, we aimed to emphasize that HT1 can present at a later age than usual. The age of onset and the clinical presentation can be variable between members of the same family, with the same genotype, and it could be presented with unusual presentation. In general, there was no clear correlation observed between clinical presentation and genotype.

Acute and chronic forms have been observed in the same family, as well as in some unrelated individuals with the same genotype. One mechanism that could explain this clinical variety is the hypothesis of gene reversion. A study of hepatic nodules removed from livers of individuals affected with the chronic form of HT1 showed that some cells tested positive for FAH protein and have residual enzymatic activity for FAH. These seemingly "normal" cells appear to have arisen by the mechanism of gene reversion, that is, the spontaneous self-correction of the pathogenic germline variant to the normal sequence of the gene during somatic cell division (9). These hepatic foci of revertant "normal" cell colonies comprise many of the liver nodules founded in untreated individuals who have chronic HT1, who were manifesting milder biochemical and clinical presentation, but the continued production of toxic metabolites by the non-revertant mutated cells increases the risk for malignant transformation to hepatocellular carcinoma. Epigenetic and/or environmental factors could play an important role in modulating the phenotype in HTI, and therefore the relationship between phenotype and genotype is not straightforward and remains to be fully elucidated (2,9). The variant identified in our patient was a nonsense variant and has been reported previously along with a second pathogenic FAH variant (c.938delC) in a patient with HT1 (9). This patient presented with mostly neurological manifestations (hypotonia and some pain crises), which was correlated well with his very high levels (720 mmol/mol creat. Normal: 0-3) of 5-ALA at diagnosis (9). The reason for seizures in our patients was not clear. It could be a coincidence, given seizure disorders were relatively more common than HT1. Alternatively, they could be part of a neurological crisis, although 5-ALA was not measured to prove this possibility. Moreover, seizures started after treatment with nitisinone were initiated for a few months, and therefore this was expected to lower 5-ALA levels.

Conclusion

In conclusion, we presented a patient with an unusual, late presentation of HT1. This case highlights a few principles that could help in diagnosing patients with IEM. First, the presentation of IEM could be not typical, and therefore an index of suspicion should always be there. Second, family history is a very important element in approaching patients with suspected IEM. Finally, it was worth evaluating treatable IEM first, like tyrosinemia, as early treatment could prevent significant long-term complications.

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List of Abbreviations

FAH	Fumarylacetoacetate hydrolase
HT1	Hereditary tyrosinemia type I
NBS	Newborn screening
SA	Succinylacetone

Conflict of interest
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Consent for publication
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Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

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