Rare disease

Persistent coagulopathy during *Escherichia coli* sepsis in a previously healthy infant revealed undiagnosed tyrosinaemia type 1

H Georgouli,¹ K H Schulpis,² H Michelakaki,³ M Kaltsa,¹ T Sdogou,¹ L Kossiva¹

¹Second Department of Pediatrics, P&A, Kyriakou, Children's Hospital, Athens University, Athens, Greece;

²Institute of Child Health, 'Aghia Sophia' Children's Hospital, Athens, Greece;

³Department of Enzymology and Cellular Function, Institute of Child Health, 'Aghia Sophia' Children's Hospital, Athens, Greece

Correspondence to L Kossiva, lydiakossiva@hotmail.com

SUMMARY

Hereditary tyrosinaemia type 1 (HT1) is caused by an enzymatic defect in tyrosine metabolism. It is an autosomal recessive disorder and affects both sexes equally. In young infants HT1 can present as severe liver involvement and in older infants as liver failure and renal tubular dysfunction together with growth failure and rickets. The authors report the case of a 5-month-old, previously healthy, male infant who presented with *Escherichia coli* sepsis and severe coagulopathy due to liver dysfunction. Despite the early diagnosis of HT1 and treatment with 2-(2-nitro-4-trifluoromethylbenzoyl)-1, 3-cyclohexanedione (NTBC), the patient died from severe coagulopathy and multi-organ failure.

BACKGROUND

Tyrosinaemia type 1 is an extremely rare condition in southern Europe, and leads to death if untreated. In infancy, tyrosinaemia type 1 can manifest as persistent bleeding diathesis due to liver failure. A high degree of suspicion is required for early recognition and treatment of hereditary tyrosinaemia type 1 (HT1) in an infant presenting with sepsis and severe coagulopathy resistant to replacement treatment with fresh frozen plasma. It is noteworthy that until his admission our patient was a healthy and well-nourished child without hepatomegaly or signs of bleeding diathesis.

CASE PRESENTATION

Introduction

It is well recognised that HT1 may present in infancy with liver and renal dysfunction.¹ An additional major problem is the severe impairment of the synthesis of clotting factors leading to bleeding diathesis which in combination with sepsis can be devastating. We present the case of a previously well 5-month-old infant with sepsis from *Escherichia coli* and severe persistent coagulopathy attributable to HT1.

Case presentation

A 5-month-old white male infant presenting with high fever, vomiting and irritability was admitted to the hospital for investigation. He was the only child of non-consanguineous parents of Greek origin, born full term with a birth weight of 3 kg and normal perinatal period. His paediatrician reported no problems during routine vaccination visits with no signs of bleeding diathesis at the sites of injection.

INVESTIGATIONS

On initial assessment the child's weight was 6.5 kg (50th percentile) and height was 64 cm (75th percentile). Physical examination revealed distension of the abdomen with hepatomegaly (3 cm under the right costal margin) without palpable spleen or ascites. The rest of the evaluation was normal.

On laboratory work up, complete blood count revealed haemoglobin 10.6 g/dl, white blood cell count 16 600/mm³ (neutrophils 68%, lymphocytes 27%, monocytes 5%) and platelets 142 000/mm³, and biochemistry revealed serum glutamic oxaloacetic transaminase 93 U/l, serum glutamic pyruvic transaminase 48 U/l, alkaline phosphatase (ALP) 2486 U/l, glucose 58 mg/dl, protein 3.8 mg/dl, albumin 2.7 mg/dl, calcium 8.5 mg/dl (8.6–10.6 mg/dl), serum phosphorus 2 mg/dl (>4 mg/dl), bilirubin 3 mg/dl, blood urea nitrogen 8 mg/dl and creatinine 0.3 mg/dl. The coagulation profile was significantly disturbed (table 1). Blood cultures taken on admission were positive for *E coli*.

Ultrasound evaluation of the abdomen revealed enlargement of both hepatic lobes with multiple hepatic hypoechoic lesions of variable size. The bile duct had oedema and the kidneys were slightly enlarged with increased ultrasonic density. The hepatic lesions were considered to be abscesses. A CT scan showed low density lesions in both lobes of the liver. Unfortunately, a liver biopsy could not be conducted due to severe and persisting coagulopathy.

DIFFERENTIAL DIAGNOSIS

The most likely diagnosis was abscesses due to *E coli* sepsis but a more extensive laboratory work up for galactosaemia was negative. Chronic granulomatous disease which can also cause liver abscesses was excluded based

Table 1 Coagulation profile

	Day 0	Day 1	Day 7	Day 16
PT	54.2	58.2	53	88.8
aPTT	44.3	74.5	99.6	117.1
INR	4.9	5.3	4.8	8.3
D-dimers, $\mu\text{g/l}$	296.8	653.5	627.7	273.2
Fibrinogen	1	1.2		0.6

INR, international normalised ratio; PT, prothrombin time; aPTT, activated partial thromboplastin time.

on the normal immunophenotype of peripheral blood and normal levels of immunoglobulins, C3 and C4 and a normal dihydrorhodamine test. Serum α -fetoprotein was markedly elevated (108 875 ng/ml) indicating either neoplasia or metabolic disease. High serum methionine (696 mmol/l) and tyrosine (493 mmol/l) in combination with the α -fetoprotein level and persistent coagulopathy despite replacement treatment with fresh frozen plasma and vitamin K, raised the suspicion of tyrosinaemia. The increased amounts of succinyl acetone in plasma and urine were pathognomonic for hepatorenal tyrosinaemia. Molecular genetic analysis confirmed the diagnosis. Our patient was found to be homozygous for the c.1A>G mutation in exon 1 of the fumarylacetoacetate hydrolase (FAH) gene. Homozygosity for this mutation is associated with HT1. Both parents were heterozygous carriers of the mutation.

TREATMENT

Even though sepsis was under control and specific therapy with 2-(2-nitro-4-trifluoromethylbenzoyl)-1, 3-cyclohexanedione (NTBC) was started immediately after diagnosis, our patient showed haemodynamic instability and irreversible metabolic acidosis along with hyperammoniaemia.

OUTCOME AND FOLLOW-UP

The patient died a few days later from severe liver failure with prolonged clotting times and lung haemorrhage. Postmortem findings showed lung haemorrhage (shock lung) and regenerating cirrhotic hepatic nodules with increased fibrin, fatty infiltration and vacuolar degeneration of hepatic cells.

DISCUSSION

HT1, also known as hepatorenal tyrosinaemia, belongs to a group of rare congenital metabolic disorders and is inherited as an autosomal recessive trait. HT1 is the most severe disorder of tyrosine metabolism and is caused by a deficiency of FAH, leading to accumulation of the intermediate toxic metabolite fumarylacetoacetate (FAA), which is converted into two metabolites, succinyl acetoacetate and succinyl acetone, that are released into the circulation and thus can be measured for the diagnosis.^{1 2} Free fatty acids accumulate in hepatocytes and proximal renal tubular cells, resulting in liver and kidney damage. Succinyl acetone is also responsible for acute neurological symptoms. The disease is caused by mutations in the FAH gene,

located on the long arm of chromosome 15 (15q23–q25).³ The global frequency of tyrosinaemia is 1/100 000, with Scandinavia and Quebec in Canada having a higher frequency (0.8/1000).⁴ There are two forms of tyrosinaemia, an acute and a chronic. In the acute form, affected individuals present in the first months of life with failure to thrive, vomiting, jaundice, hepatomegaly and splenomegaly. Severe liver involvement is characterised by acute hepatic crises triggered by infections or catabolic stress conditions.⁵ Symptoms of acute hepatic crisis include hypoglycaemia, vomiting, diarrhoea, gastrointestinal bleeding, coagulation abnormalities, irritability, lethargy and fever. Without treatment most infants die in the first year of life due to hepatic failure.⁶

It is noteworthy that our patient was a well-nourished infant without previous hospitalisation or bleeding after vaccination who presented with *E coli* sepsis and severe liver dysfunction. An infection in an HT1 patient may trigger a life-threatening hepatic crisis. Coagulopathy is a well-described complication of HT1.⁷ The serum α -fetoprotein level is elevated in patients with tyrosinaemia type 1 and its measurement can be used as a screening tool.⁸ Our patient had also elevated ALP and extremely low phosphorus levels which could be attributed to renal tubular damage and early rickets. Tyrosinaemia should be suspected in any infant or child with decreased hepatic synthetic function, especially with an abnormal coagulation profile without evident cause, and markedly elevated blood α -fetoprotein and urine succinyl acetone. Transaminases and bilirubin in these patients are modestly elevated if at all. Some patients with tyrosinaemia present with bleeding without other hepatic signs and are investigated initially for a primary haematological problem. Prothrombin and partial thromboplastin times may be extremely prolonged, even in apparently well infants.⁷ It is noteworthy that vitamin K supplementation does not correct these abnormalities.

To conclude, HT1 is a very rare disease but should be considered in any infant with evidence of deteriorated liver function with coagulopathy unresponsive to vitamin K and frozen plasma administration. The presence of hypophosphataemic rickets or other tubular disorders is strongly indicative of HT1, especially if associated with abnormal liver function.

This case highlights the high degree of suspicion for HT1 required in any infant with sepsis and severe coagulopathy, even though the past medical history of the patient is uneventful.

Learning points

- ▶ Tyrosinaemia type 1 may manifest as abrupt liver failure in a previously healthy and well-nourished infant.
- ▶ Serum α -fetoprotein and succinyl acetone plasma and urine levels can be used for detecting tyrosinaemia type 1, while plasma tyrosine levels are not a reliable indicator.
- ▶ A markedly elevated α -fetoprotein level with a prolonged prothrombin time/partial thromboplastin time are strong indicators of tyrosinaemia type 1.
- ▶ When evaluating liver lesions in infants with sepsis, metabolic diseases should be included in the differential diagnosis.

Competing interests None.

Patient consent Obtained.

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