CASE REPORT

Hypomorphic citrullinaemia due to mutated *ASS1* with episodic ataxia

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SUMMARY

Children with citrullinaemia commonly present in the neonatal period with life-threatening hyperammonaemia and progressive encephalopathy. Less often, 'hypomorphic' or mild late-onset childhood or adult-onset forms may be seen with intermittent neurological symptoms or acute crisis in pregnancy. We describe an 11-year-old boy with late-onset citrullinaemia manifesting as brief episodes of ataxia triggered by minor febrile illnesses, significant citrullinaemia, mild hyperammonaemia, normal neurological examination and mild cerebellar atrophy. Targeted gene sequencing showed a homozygous, missense mutation c.815G>A (p.R272H) in exon 12 of *ASS1* gene resulting in the amino acid substitution of histidine for arginine at codon 272. Our case highlights the importance of recognising urea cycle defects as a cause of intermittent neurological symptoms such as ataxia. Type-1 citrullinaemia may remain hypomorphic and needs a high index of suspicion.

BACKGROUND

Citrullinaemia is a rare, autosomal-recessive disorder of urea cycle caused by mutations in the *ASS1* (type I citrullinaemia) and *SLC25A13* (type II citrullinaemia or citrin deficiency) genes. Mutations in the *ASS1* gene on chromosome 9q34 cause deficiency of argininosuccinate synthetase enzyme. This enzyme catalyses the formation of argininosuccinic acid from citrulline and aspartic acid. The disorder commonly presents in neonates with acute life-threatening hyperammonaemia and progressive encephalopathy. Less often, 'hypomorphic' or mild late-onset childhood or adult-onset forms may be seen with intermittent neurological symptoms (headaches, vision impairment, strokes, intellectual disability, tone and motor problems, ataxia or encephalopathy), chronic or recurrent hyperammonaemia or acute crisis in pregnancy. Infrequently, incidental citrullinaemia has been detected in asymptomatic individuals without hyperammonaemia.¹

We describe an 11-year-old boy with late-onset, hypomorphic Type-1 citrullinaemia manifesting as brief episodes of ataxia after minor febrile illnesses, citrullinaemia, hyperammonaemia, normal neurological examination and cerebellar atrophy. Genetic analysis confirmed a homozygous, missense mutation c.815G>A (p.R272H) in exon 12 of *ASS1* gene. Our case highlights that urea cycle defects should be considered among the causes of

intermittent neurological symptoms. Early identification helps in the institution of appropriate therapy and prevention of episodic symptoms and hyperammonaemia.

CASE PRESENTATION

An 11-year-old, developmentally normal boy presented with a history of two episodes of incoordination and gait imbalance following minor febrile illnesses over the past 4 months. Fever was mild, brief in duration and non-localising. The incoordination and gait imbalance were acute in onset and remitted in 7 days. There was no associated vomiting, headache, alteration in sensorium, sleep disturbance, seizures, focal motor deficits, extrapyramidal movements, nystagmus, skin rash or abnormal body odour. He remained well in between the episodes and was asymptomatic at presentation. He was born to non-consanguineous parents by an uneventful term, vaginal delivery. The personal and family history was unremarkable. On examination, he had normal head circumference (51.5 cm) and mild pallor. Rest of the systemic examination was unremarkable. His intelligence was normal (IQ 95). No psychopathology was detected on childhood psychopathology measurement schedule and no behavioural abnormalities were detected on child behaviour checklist.

INVESTIGATIONS

Laboratory investigations showed normal pH (7.4), anion gap (6.5), alpha-fetoprotein levels (<10 IU/mL) and homocysteine levels (10 µmol/L, normal range 5–15 µmol/L). MRI of the brain showed mild cerebellar atrophy with an incidental left parasagittal calcified neurocysticercosis. A diagnosis of acute, intermittent ataxia secondary to an underlying neurometabolic disorder was considered. Grossly elevated citrulline levels were noted on tandem mass spectroscopy 1853 µmol/L (normal <45 µmol/L) and high-performance liquid chromatography 1986 µmol/L (normal 8–47 µmol/L). Plasma glutamine was 675 µmol/L (normal 333–809 µmol/L). Plasma arginine was 11 µmol/L (normal 12–112 µmol/L) and ammonia was 208 µmol/L (normal <70 µmol/L for age). Plasma argininosuccinic acid was undetectable and urinary organic acids were normal. Targeted gene sequencing using next-generation sequencing showed a homozygous, missense mutation in the exon 12 of *ASS1* gene (chr9:133355813; G>A) that resulted in the amino acid substitution of histidine for arginine at codon 272 (p.R272H; ENST00000372394).

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TREATMENT

He was started on oral sodium benzoate (2500 mg/day), oral arginine (2500 mg/day) and protein-restricted diet to prevent further episodes.

OUTCOME AND FOLLOW-UP

At 1 year follow-up, he was well and there had been no recurrence of neurological symptoms. His plasma ammonia ranged between 40 and 60 $\mu\text{mol/L}$ after treatment.

DISCUSSION

The biochemical findings of hyperammonaemia ($>150 \mu\text{mol/L}$; may range to $\geq 2000\text{--}3000 \mu\text{mol/L}$) and citrullinaemia (usually $>1000 \mu\text{mol/L}$) establish the diagnosis of type 1 citrullinaemia.² However, the clinical course, severity and prognosis are difficult to predict based on biochemical results alone, especially in the late-onset forms. In vitro expression studies have shown that milder forms of type 1 citrullinaemia may be due to kinetic variants of well-folded ASS enzyme or differential residual activity of the defective enzyme and routine enzyme studies may miss these milder forms, hence genetic studies are desirable to detect the paucisymptomatic or hypomorphic forms.³

The homozygous missense mutation c.815G>A (p.R272H) seen in our patient has been anecdotally reported in a compound heterozygous state in literature and has been identified as 'possibly damaging' by PolyPhen and Sorting Intolerant from Tolerant (SIFT) prediction.⁴ A 'hypomorphic' infant of Indian origin, detected to have citrullinaemia on expanded newborn screening, remained asymptomatic with normal cognitive development at 1 year of age on modestly protein restricted diet.⁴ Mutation analysis of ASS1 gene in this patient demonstrated compound heterozygous mutations: c.1168G>A (p.G390R) and c.815G>A (p.R272H).⁴ Another 22-month-old Caucasian boy with developmental delay and a severe clinical presentation with acute liver failure due to type 1 citrullinaemia showed the same mutation in a compound heterozygous state: c.685del8bp (fs232X) and c.815G>A (p.R272H) in the ASS gene.⁵ Hence, it is difficult to derive genotype-phenotype correlations in children with type 1 citrullinaemia. Our patient presented with a milder phenotype despite harbouring the 'possibly damaging' mutation in homozygous state and has been asymptomatic in follow-up for 1 year now on treatment.

Children with type 1 citrullinaemia need both acute and chronic management plans. In the acute state, the main goals are a rapid reduction of hyperammonaemia using either pharmacological nitrogen scavenger therapy (sodium benzoate, sodium phenylacetate and arginine) or haemodialysis, reversal of catabolism (intravenous glucose infusion, intralipids or

protein-free enteral nutrition) and control of intracranial hypertension. Chronic management includes protein-restricted diet and oral nitrogen scavengers (sodium phenylbutyrate/benzoate) to maintain plasma ammonia concentration $<100 \mu\text{mol/L}$ and normal plasma glutamine concentration.² Children need regular follow-up to monitor for hyperammonaemia, secondary deficiency of essential amino acids, to ensure early medical attention during intercurrent infections/stressful periods and possible hypertrophic cardiomyopathy and bilateral cataracts in adolescence.¹ The index patient has remained well in follow-up for 1 year now on modestly protein-restricted diet and oral sodium benzoate therapy.

Learning points

- Urea cycle defects are important causes of intermittent neurological symptoms.
- First report of homozygous presentation of c.815G>A (p.R272H) mutation in late-onset type 1 citrullinaemia from India.
- Early identification helps in the institution of appropriate therapy and prevention of episodic symptoms and hyperammonaemia.

Contributors AGS: patient management, draft of manuscript and review of literature. SA: analysis and interpretation of biochemical data and manuscript editing. NS: critical review of manuscript for intellectual content. PS: clinician-in-charge and critical review of manuscript for intellectual content and final approval of the version to be published.

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