ePO06

Homocystinuria in an adolescent patient with Chr21q22.2q22.3 deletion

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Background: Homocystinuria is characterized by skeletal manifestations (tall stature, dolichostenomelia, scoliosis, and pectus excavatum), ophthalmologic problems (ectopia lentis, severe myopia), vascular thromboembolism, and intellectual disability. Other features sometimes seen include: seizures, psychiatric problems, extrapyramidal signs, hypopigmentation of the skin and hair, malar flush, livedo reticularis, and pancreatitis.
Homocystinuria is caused by biallelic pathogenic variants in the *CBS* gene which encodes the cystathionine β-synthase enzyme. Biochemical findings include elevated urine homocystine, elevated plasma total homocysteine, homocystine, and methionine.
Case presentation: Here we present the case of a 14-year-old male of Italian descent who presented to the office of medical genetics after being referred for evaluation of suspected Marfan syndrome. His medical history was significant for life-long hypotonia, inguinal hernia, mild intellectual disability, mitral valve prolapse, proximal muscle wasting, lens dislocation, and joint contractures. On physical examination he was noted to have a Marfanoid habitus with pectus excavatum. Chromosome microarray revealed a 5.9 Mb interstitial deletion of arr [grch37] 21q22.2q22.3(40648264_46505895)x1. This chromosomal deletion is associated with developmental delay and intellectual disability. The deleted region includes the DSCAM gene, noted as a risk factor for autism spectrum disorder when haploinsufficient. This deletion also contains the CBS gene. Additional genetic testing revealed a pathogenic variant in the non-deleted allele of the CBS gene NM_000071.3:c.833T>C, LRG_777p1:p.Ile278Thr which confirmed the diagnosis of autosomal recessive Homocystinuria due to cystathionine beta-synthase deficiency.
Biochemical evaluation revealed a plasma homocysteine level of >250 umol/L (N=<15 umol/L) and serum Methionine 669 umol/L (13.9-36.5).
Conclusion: The patient was treated with a methionine free formula (Homactin AA) and low protein diet (1.2 gm/kg), Betaine, and supplemental B6. Plasma homocysteine level with treatment decreased to 16.6umol/L. The patient reported subjective improvements in sleep and focus. Homocystinuria should be kept in the differential diagnosis of all patients with unexplained Marfanoid habitus and/or ectopia lentis, even when presenting at an older age without thromboembolism.

https://doi.org/10.1016/j.gim.2022.01.044

ePO07

Delayed onset hyperammonemic encephalopathy in an adult with GLUD1 deficiency

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Background: Hyperammonemic encephalopathy is characterized by altered mental status due to toxic accumulation of ammonia in the circulation. Prolonged hyperammonemia can result in persistent seizures, cerebral edema, coma, and death. Therefore, prompt evaluation for underlying cause and initiating appropriate therapy is crucial in the management of this condition. In adults, common causes of hyperammonemia include hepatic dysfunction, infections, portosystemic shunting, and medications like valproic acid. Rarely, urea cycle defects and organic acidemias may present in the adulthood. GLUD1 deficiency is an autosomal dominant condition that is associated with infantile onset hyperinsulinemic hypoglycemia and hyperammonemia. *GLUD1* encodes for glutamate dehydrogenase (GDH), which plays an important role in the mitochondria in glutamate metabolism by converting it to α-ketoglutarate and ammonia. Pathogenic variants in *GLUD1* result in decreased sensitivity to guanosine-5'-triphosphate (GTP), which is a direct inhibitor of this enzyme. Consequently, this results in fasting-induced and protein meal-induced hyperinsulinemic hypoglycemia and hyperammonemia. We describe a unique case of hyperammonemic encephalopathy due to GLUD1 deficiency presenting in an older adult.
Case presentation: A 60-year-old female presented to our hospital with altered mental status and status epilepticus. Her initial laboratory evaluation revealed a high anion gap metabolic acidosis and an elevated lactate, both of which normalized after controlling her seizures. She had a normal blood sugar level and liver function tests. Interestingly, she had persistently elevated ammonia levels in the range of 70-130 μM /L. Her past medical history was significant for childhood-onset epilepsy, intellectual disability, hypothyroidism, hyperlipidemia, and type 2 diabetes mellitus. Her pediatric history was significant for multiple evaluations for recurrent hypoglycemic attacks associated with inappropriately elevated insulin levels. Her family history was unremarkable. One of the initial considerations during the admission was valproate-induced hyperammonemia. However, her ammonia remained mildly elevated despite switching valproic acid to levetiracetam. Her metabolic workup revealed a low plasma citrulline, low free and total carnitine and mildly elevated urine orotic acid. Her molecular panel testing for urea cycle disorders was negative. Based on her pediatric history of hyperinsulinism, we performed molecular testing to exclude GLUD1 deficiency. *GLUD1* gene sequencing revealed a pathogenic variant (NM_005271.5: c.820C>T, p.Arg274Cys), confirming the diagnosis of autosomal dominant hyperinsulinism-hyperammonemia syndrome.
Conclusion: We report an unusual presentation of GLUD1 deficiency in an adult patient with hyperammonemic encephalopathy. Although inborn errors of metabolism primarily manifest in the pediatric age group, they may present with a highly variable clinical phenotype in adults. Therefore, it is crucial to consider these disorders in adults presenting with unexplained metabolic derangements such as persistent hyperammonemia. Rapid access to molecular testing using next generation sequencing technologies is slowly becoming instrumental in establishing diagnoses in rare metabolic disorders.

https://doi.org/10.1016/j.gim.2022.01.045