

# Diagnosis and Genetic Analysis of Glutaric Acidaemia Type I

Very rarely seen inborn error of metabolism

التشخيص و التحليل الوراثي لجلوتاريك احمضاض الدم النوع 1

خطأ استقلابي وراثي نادرا جدا

Sir,

A 10-month-old female child with delayed milestones presented to the genetic clinic of the Fernandez Hospital in Hyderabad, India, in January 2008. She had been delivered at full term via a lower segment Caesarean section due to non-progressive labour. The head circumference at birth was 33 cm and the baby cried immediately after birth with Apgar scores of 8, 9 and 9 at one, five and 10 minutes, respectively. The family were Muslim and of Indian descent and the child had been raised in India. The parents reported a history of stiffness in the child's hands occurring intermittently for the previous two months; a cold, cough and fever over the preceding eight days; and regression of developmental milestones.

A physical examination revealed that the child was conscious and alert with a head circumference of 54.5 cm (>90<sup>th</sup> percentile). Neurological examination of the infant revealed increased muscle tone in all of the limbs with exaggerated deep reflexes. The complete blood count and serum electrolyte and serum calcium levels were normal. An electroencephalogram displayed a normal pattern. The metabolic work-up revealed elevated glutaric, glutaconic and 3-hydroxyglutaric acids in the urine. Magnetic resonance imaging of the brain showed bilateral hyperintense signal abnormalities in the basal ganglia with symmetrical involvement of the lenticular and caudate nuclei and thalamic hypointensity. There was evidence of diffuse cerebral cortical atrophy with wide extra-axial cerebrospinal fluid spaces in the frontal and temporal regions. Superior centrum semiovale white matter hypointense *foci* were also observed. Magnetic resonance spectroscopy showed patterns of high glutamate and minimal lactate production and a normal choline/creatinine ratio.

Sanger sequencing of the *glutaryl-coenzyme A dehydrogenase (GCDH)* gene revealed that the child had a homozygous mutation c.1119T>G (p. N373K) in exon 10. Both of the infant's parents were heterozygous for the same mutation. During their subsequent pregnancy, the couple were followed-up by the clinic staff and the fetus was tested for the *GCDH* gene. The results suggested that the fetus was heterozygous for the mutation. The pregnancy was continued and further screening after birth indicated that the infant was not affected. Had the genetic testing revealed that their second child did have a homozygous mutation, the option of terminating the pregnancy would have been discussed with the parents. Genetic counselling would also have been offered to aid the parents in their decision-making.

The early diagnosis of inborn errors of metabolism (IEMs) is important not only to ensure rapid treatment of the index case but also to inform subsequent pregnancies.<sup>1,2</sup> Glutaric acidaemia type I (GAI) is an IEM whereby the body is unable to completely break down the lysine, hydroxylysine and tryptophan amino acids, resulting in the accumulation of intermediate breakdown products (such as glutaric acid, glutaryl-coenzyme A, 3-hydroxyglutaric acid and glutaconic acid) in bodily fluids and various organs, particularly the brain.<sup>3,4</sup> GAI sometimes results in mental retardation and is also known to cause secondary carnitine deficiency.<sup>5</sup> The estimated prevalence of GAI is one in 100,000 newborns.<sup>1</sup>

The presentation of GAI is variable and appears unrelated to biochemical pheno- or genotypes. Most affected neonates are asymptomatic initially, gradually developing macrocephaly as they get older, with frontal bossing from birth or during the first six months of life.<sup>6,7</sup> They typically present with symptoms of acute encephalopathy, usually secondary to a concurrent infection or due to other acute catabolic states such as diarrhoea or vomiting. This normally leads to a misdiagnosis of viral encephalopathy secondary to encephalitis or acute disseminated encephalomyelitis.<sup>6,7</sup> After the acute course, extrapyramidal symptoms will develop corresponding to the striatal involvement; this is usually seen as necrosis on neuroimaging. However, GAI can also have an insidious onset without episodes of acute deterioration; rarely, the condition presents in adulthood asymptotically or with progressive encephalopathy.<sup>6,7</sup>

Episodes of decompensation and encephalopathy are mild or absent in approximately 25% of children affected by GAI.<sup>8</sup> Typically, these patients develop dystonia (usually diagnosed as cerebral palsy), motor delay and intellectual disability.<sup>9,10</sup> Some children present with an acute subdural haemorrhage or chronic subdural effusions that may be erroneously attributed to child abuse or shaken baby syndrome. A possible explanation for acute haemorrhage is the increased fragility of bridging veins that are stretched due to cerebral atrophy.<sup>9,10</sup> Medical professionals should consider the wide presentation of this condition when assessing patients with suspected GAI.<sup>11</sup>

Clinicians should be aware of the clinical spectrum of IEM and consider these rare disorders in cases of unexplained illness, delayed milestones, global developmental delay or unexplained neonatal death as well as among patients with a family history of IEM. Early diagnosis of these conditions through newborn screening programmes can lead to improved neurodevelopmental outcomes. Genetic analysis is currently the gold standard for diagnosing IEM. All affected IEM patients should be closely followed up and comply with necessary dietary management. In cases of developmental delay, early stimulation is advisable. Treatment with carnitine and riboflavin are also beneficial treatment options.<sup>12</sup>

**Madhavi Vasikarla,<sup>1</sup> Aakash Pandita,<sup>2</sup> \*Deepak Sharma,<sup>2</sup> Oleti T. Pratap,<sup>2</sup> Srinivas Murki<sup>2</sup>**

*Departments of<sup>1</sup>Genetics and<sup>2</sup>Neonatology, Fernandez Hospital, Hyderabad, India*

*\*Corresponding Author e-mail: dr.deepak.rohtak@gmail.com*

## References

- Pfeil J, Listl S, Hoffmann GF, Kölker S, Lindner M, Burgard P. Newborn screening by tandem mass spectrometry for glutaric aciduria type 1: A cost-effectiveness analysis. *Orphanet J Rare Dis* 2013; 8:167. doi: 10.1186/1750-1172-8-167.
- Lindner M, Kölker S, Schulze A, Christensen E, Greenberg CR, Hoffmann GF. Neonatal screening for glutaryl-CoA dehydrogenase deficiency. *J Inher Metab Dis* 2004; 27:851–9. doi: 10.1023/b:boli.0000045769.96657.af.
- Harting I, Neumaier-Probst E, Seitz A, Maier EM, Assmann B, Baric I, et al. Dynamic changes of striatal and extrastriatal abnormalities in glutaric aciduria type I. *Brain* 2009; 132:1764–82. doi: 10.1093/brain/awp112.
- Hoffmann GF, Trefz FK, Barth PG, Böhles HJ, Biggemann B, Bremer HJ, et al. Glutaryl-coenzyme A dehydrogenase deficiency: A distinct encephalopathy. *Pediatrics* 1991; 88:1194–203.
- Hedlund GL, Longo N, Pasquali M. Glutaric acidemia type 1. *Am J Med Genet C Semin Med Genet* 2006; 142C:86–94. doi: 10.1002/ajmg.c.30088.
- Wen P, Wang GB, Liu XH, Chen ZL, Shang Y, Cui D, et al. [Analysis of clinical features and GCDH gene mutations in four patients with glutaric acidemia type I]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2012; 29:642–7. doi: 10.3760/cma.j.issn.1003-9406.2012.06.004.
- Strauss KA, Puffenberger EG, Robinson DL, Morton DH. Type I glutaric aciduria, part 1: Natural history of 77 patients. *Am J Med Genet C Semin Med Genet* 2003; 121:38–52. doi: 10.1002/ajmg.c.20007.
- Strauss KA, Morton DH. Type I glutaric aciduria, part 2: A model of acute striatal necrosis. *Am J Med Genet C Semin Med Genet* 2003; 121:53–70. doi: 10.1002/ajmg.c.20008.
- Funk CB, Prasad AN, Frosk P, Sauer S, Kölker S, Greenberg CR, et al. Neuropathological, biochemical and molecular findings in a glutaric acidemia type 1 cohort. *Brain* 2005; 128:711–22. doi: 10.1093/brain/awh401.
- Mühlhausen C, Ergün S, Strauss KA, Koeller DM, Crnic L, Woontner M, et al. Vascular dysfunction as an additional pathomechanism in glutaric aciduria type I. *J Inher Metab Dis* 2004; 27:829–34. doi: 10.1023/B:BOLI.0000045766.98718.d6.
- Wang Q, Ding Y, Liu Y, Li X, Wu T, Song J, et al. [Clinical and laboratory studies on 28 patients with glutaric aciduria type 1]. *Zhonghua Er Ke Za Zhi* 2014; 52:415–19.
- Kölker S, Greenberg CR, Lindner M, Müller E, Naughten ER, Hoffmann GF. Emergency treatment in glutaryl-CoA dehydrogenase deficiency. *J Inher Metab Dis* 2004; 27:893–902. doi: 10.1023/B:BOLI.0000045774.51260.ea.